COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CALCIUM MODULATING AGENT FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM DAMAGE

CROSS REFERENCE TO RELATED APPLICATION

[001] This application claims priority from Provisional Application: Serial No. 60/464,499 filed on April 22, 2003, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[002] The present invention provides compositions and methods for the treatment of central nervous system damage. More particularly, the invention is directed toward a combination therapy for the treatment or prevention of ischemic-mediated central nervous system damage including ischemic stroke, or central nervous system damage resulting from traumatic injury, comprising the administration to a subject of a calcium modulating agent in combination with a cyclooxygenase-2 selective inhibitor.

BACKGROUND OF THE INVENTION

[003] The continued increase in the incidence of ischemic-mediated central nervous system damage, including ischemic stroke, provides compelling evidence that there is a continuing need for better treatment strategies. Stroke, for example, is consistently the second or the third leading cause of death annually and the leading producer of disability among adults in the United States and western countries. Moreover, roughly 10% of patients with stroke become heavily handicapped, often needing attendant care.

[004] Within the 1990's decade, the pathology underlying ischemic-mediated central nervous system injury was elucidated. Generally speaking, the normal amount of perfusion to brain gray matter is 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs only when the flow of blood falls below a certain level (approximately 8-10 mL/100 g of brain tissue/min) while at slightly higher levels the tissue remains alive but not able to function. For example, most strokes culminate in a core area of cell death (infarction) in which blood flow is so drastically reduced that the cells usually cannot recover. This threshold seems to occur when cerebral blood flow is 20 percent of normal or less. Without neuroprotective agents, nerve cells facing 80 to 100 percent ischemia will be irreversibly damaged within a few minutes. Surrounding the ischemic core is another area of tissue called the "ischemic penumbra" or "transitional zone" in which

cerebral blood flow is between 20 and 50 percent of normal. Cells in this area are endangered, but not yet irreversibly damaged. Thus in the acute stroke, the affected central core brain tissue may die while the more peripheral tissues remain alive for many years after the initial insult, depending on the amount of blood the brain tissue receives.

[005] At the cellular level, if left untreated, rapidly within the core infarction, and over time within the ischemic penumbra, brain or spinal cell injury and death progress in stepwise manner. Without adequate blood supply, brain or spinal cells lose their ability to produce energy, particularly adenosine triphosphate (ATP). When this energy failure occurs, brain or spinal cells become damaged and will die if critical thresholds are reached. Immediate cell death within the ischemic core is typically necrotic, while cell death in the penumbra may be either necrotic or apoptotic. It is believed that there are an immense number of mechanisms at work causing brain or spinal cell damage and death following energy failure. Each of these mechanisms represents a potential route for intervention. One of the ways brain cells respond to energy failure is by elevating the concentration of intracellular calcium. Worsening this and driving the concentrations to dangerous levels is the process of excitotoxicity, in which brain cells release excessive amounts of glutamate, a neurotransmitter. This stimulates chemical and electrical activities in receptors on other brain cells, which leads to the degradation and destruction of vital cellular structures. Brain cells ultimately die as a result of the actions of calcium-activated proteases (enzymes which digest cell proteins), lipases (enzymes which digest cell membranes) and free radicals formed as a result of the ischemic cascade.

[006] Interventions have been directed toward salvaging the ischemic penumbra and reducing its size. Restoration of blood flow is the first step toward rescuing the tissue within the penumbra. Therefore, timely recanalization of an occluded vessel to restore perfusion in both the penumbra and in the ischemic core is one treatment option employed. Partial recanalization also markedly reduces the size of the penumbra as well. Moreover, intravenous tissue plasminogen activator and other thrombolytic agents have been shown to have clinical benefit if they are administered within a few hours of symptom onset. Beyond this narrow time window, however, the likelihood of beneficial effects is reduced and hemorrhagic complications related to thrombolytic agents become excessive, seriously compromising their therapeutic value. Hypothermia decreases the size of the ischemic insult in both anecdotal clinical and laboratory reports. In addition, a wide variety of agents have been shown to reduce infarct volume in animal models. These agents include pharmacologic interventions that involve thrombolysis, calcium channel blockade, and cell membrane

receptor antagonism have been studied and have been found to be beneficial in animal cortical stroke models. But there is a continuing need for improved treatment regimes following ischemic-mediated central nervous system injury.

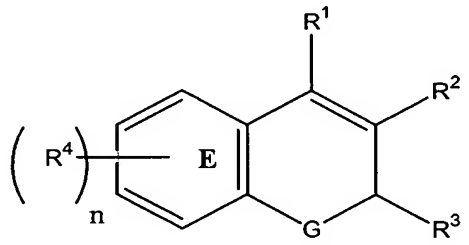
[007] Neuroprotective agents have been shown to extend the time during which neurons within the ischemic penumbra remain viable (Albers, (1997) Am. J. Cardiol. 804(4C):4d-10d). Toward that end, several studies indicate that treatment with a calcium modulating agent following ischemic-mediated central nervous system injury may be beneficial. Calcium modulating agents have been shown to significantly ameliorate neuronal injury due to transient forebrain ischemia. (Kobayashi T., et al., (2003) Brain Res. (960)(1-2):62-70). Furthermore, it has been suggested that several calcium modulating agents have shown neuroprotective effect in animal models of ischemia. In one study, for example, it was demonstrated that calcium modulating agent administration to infarcted rats showed significant neuroprotective (Burns LH, et al., (1999) J Vasc Surg 30(2):334-43). Another study demonstrated a significant improvement in reperfusion function to ischemic rats administered a calcium modulating agent compared to control animals receiving saline (Grover GJ, et al., (1989) J. Pharmacol. Exp. Ther. (251)(1):98-104).

[008] Several studies indicate that cyclooxygenase-2 is involved in the inflammatory component of the ischemic cascade. Cyclooxygenase-2 expression is known to be induced in the central nervous system following ischemic injury. In one study, it was shown that treatment with a cyclooxygenase-2 selective inhibitor reduced infarct volume in mice subjected to ischemic brain injury (Nagayama et al., (1999) J. Cereb. Blood Flow Metab.19(11):1213-19). A similar study showed that cyclooxygenase-2 deficient mice have a significant reduction in brain injury produced by occlusion of the middle cerebral artery when compared to mice that express cyclooxygenase-2 (Iadecola et al., (2001) PNAS 98:1294-1299). Another study demonstrated that treatment with cyclooxygenase-2 selective inhibitor results in improved behavioral deficits induced by reversible spinal ischemia in rabbits (Lapchak et al., (2001) Stroke 32(5):1220-1230).

SUMMARY OF THE INVENTION

[009] Among the several aspects of the invention is provided a method and a composition for the treatment of reduced blood flow to the central nervous system in a subject. The composition comprises a cyclooxygenase-2 selective inhibitor and a calcium modulating agent and the method comprises administering the composition to a subject.

[010] In one embodiment, the cyclooxygenase-2 selective inhibitor is a member of the chromene class of compounds. For example, the chromene compound may be a compound of the formula:



(I)

[011] wherein:

[012] n is an integer which is 0, 1, 2, 3 or 4;

[013] G is O, S or NR^a;

[014] R^a is alkyl;

[015] R^1 is selected from the group consisting of H and aryl;

[016] R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

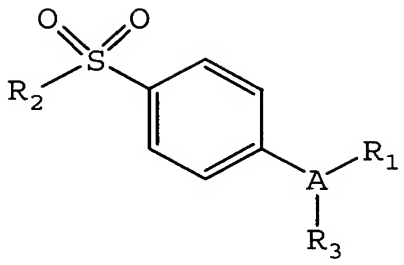
[017] R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

[018] each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

[019] or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical;

[020] or prodrug thereof.

[021] In another embodiment, the cyclooxygenase-2 selective inhibitor is a compound of the formula:



[022] wherein:

[023] A is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

[024] R_1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R_1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

[025] R_2 is selected from the group consisting of methyl or amino; and

[026] R_3 is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl.

[027] In another embodiment the calcium modulating agent inhibits the intracellular passage of calcium ions through a voltage gated membrane channel. In one alternative of this embodiment, the voltage gated membrane channel is a high-voltage activated channel. In another alternative of this embodiment, the voltage gated membrane channel is a low-voltage activated channel.

[028] In still another embodiment, the calcium modulating agent inhibits the intracellular passage of calcium ions through a receptor operated membrane channel.

[029] In yet another embodiment, the calcium modulating agent is a calcium chelating agent.

[030] Other aspects of the invention are described in more detail below.

ABBREVIATIONS AND DEFINITIONS

[031] The term "acyl" is a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, and trifluoroacetyl.

[032] The term "alkenyl" is a linear or branched radical having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl.

[033] The terms "alkenyl" and "lower alkenyl" also are radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. The term "cycloalkyl" is a saturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[034] The terms "alkoxy" and "alkyloxy" are linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

[035] The term "alkoxyalkyl" is an alkyl radical having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

[036] The term "alkoxycarbonyl" is a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower

alkoxycarbonyl" radicals with alkyl porions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

[037] Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" is a linear, cyclic or branched radical having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

[038] The term "alkylamino" is an amino group that has been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

[039] The term "alkylaminoalkyl" is a radical having one or more alkyl radicals attached to an aminoalkyl radical.

[040] The term "alkylaminocarbonyl" is an aminocarbonyl group that has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above.

[041] The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl.

[042] The term "alkylthio" is a radical containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio.

[043] The term "alkylthioalkyl" is a radical containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl

radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl.

[044] The term "alkylsulfinyl" is a radical containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

[045] The term "alkynyl" is a linear or branched radical having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

[046] The term "aminoalkyl" is an alkyl radical substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like.

[047] The term "aminocarbonyl" is an amide group of the formula -C(=O)NH2.

[048] The term "aralkoxy" is an aralkyl radical attached through an oxygen atom to other radicals.

[049] The term "aralkoxyalkyl" is an aralkoxy radical attached through an oxygen atom to an alkyl radical.

[050] The term "aralkyl" is an aryl-substituted alkyl radical such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

[051] The term "aralkylamino" is an aralkyl radical attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" are amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

[052] The term "aralkylthio" is an aralkyl radical attached to a sulfur atom.

[053] The term "aralkylthioalkyl" is an aralkylthio radical attached through a sulfur atom to an alkyl radical.

[054] The term "aroyl" is an aryl radical with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted.

[055] The term "aryl," alone or in combination, is a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

[056] The term "arylamino" is an amino group, which has been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

[057] The term "aryloxyalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent oxygen atom.

[058] The term "arylthioalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

[059] The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", is -(C=O)-.

[060] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", is $-CO_2H$.

[061] The term "carboxyalkyl" is an alkyl radical substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which are lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl.

[062] The term "cycloalkenyl" is a partially unsaturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl, and cyclohexenyl.

[063] The term "cyclooxygenase-2 selective inhibitor" is a compound able to inhibit cyclooxygenase-2 without significant inhibition of cyclooxygenase-1. Typically, it includes compounds that have a cyclooxygenase-2 IC_{50} of less than about 0.2 micro molar,

and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more typically, of at least 100. Even more typically, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 micro molar, and more preferably of greater than 10 micro molar. Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid used in the present method may inhibit enzyme activity through a variety of mechanisms. By the way of example, and without limitation, the inhibitors used in the methods described herein may block the enzyme activity directly by acting as a substrate for the enzyme.

[064] The term "halo" is a halogen such as fluorine, chlorine, bromine or iodine.

[065] The term "haloalkyl" is a radical wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically included are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" is a radical having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

[066] The term "heart disease" is used in the general sense and includes conditions ranging, for example, from those in which positive inotropic medications are useful to those in which coronary vessel occlusion is predominant, to arrhythmias or cardiotoxicity, such as that which may be observed as a side effect of cardiotoxic drugs, e.g., doxorubicin. In these conditions, it is evident that COX-2 expression and the inflammation that is attendant therewith contribute to the overall disease state. In particular, the term "heart disease" encompasses congestive heart failure.

[067] The term "heteroaryl" is an unsaturated heterocyclyl radical. Examples of unsaturated heterocyclyl radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl,

indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also includes radicals where heterocyclyl radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino.

[068] The term "heterocyclyl" is a saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radical, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

[069] The term "heterocyclylalkyl" is a saturated and partially unsaturated heterocyclyl-substituted alkyl radical, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

[070] The term "hydrido" is a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical.

[071] The term "hydroxyalkyl" is a linear or branched alkyl radical having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

[072] The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product; that is the "pharmaceutically acceptable" material is relatively safe and/or non-toxic, though not necessarily providing a separable therapeutic benefit by itself. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiologically acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[073] The term "prodrug" refers to a chemical compound that can be converted into a therapeutic compound by metabolic or simple chemical processes within the body of the subject. For example, a class of prodrugs of COX-2 inhibitors is described in US Patent No. 5,932,598, herein incorporated by reference.

[074] The term "subject" for purposes of treatment includes any human or animal subject who is in need of such treatment. The subject can be a domestic livestock species, a laboratory animal species, a zoo animal or a companion animal. In one embodiment, the subject is a mammal. In another embodiment, the mammal is a human being.

[075] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, is a divalent radical $-SO_2-$. "Alkylsulfonyl" is an alkyl radical attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower

alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" are NH_2O_2S-.

[076] The phrase "therapeutically-effective" is intended to qualify the amount of each agent (i.e. the amount of cyclooxygenase-2 selective inhibitor and the amount of calcium modulating agent) which will achieve the goal of improvement in disorder severity and the frequency of incidence over no treatment or treatment of each agent by itself.

[077] The term "thrombotic event" or "thromboembolic event" includes, but is not limited to arterial thrombosis, including stent and graft thrombosis, cardiac thrombosis, coronary thrombosis, heart valve thrombosis, pulmonary thrombosis and venous thrombosis. Cardiac thrombosis is thrombosis in the heart. Pulmonary thrombosis is thrombosis in the lung. Arterial thrombosis is thrombosis in an artery such as a carotid artery thrombosis. Coronary thrombosis is the development of an obstructive thrombus in a coronary artery, often causing sudden death or a myocardial infarction. Venous thrombosis is thrombosis in a vein. Heart valve thrombosis is a thrombosis on a heart valve. Stent thrombosis is thrombosis resulting from and/or located in the vicinity of a vascular stent. Graft thrombosis is thrombosis resulting from and/or located in the vicinity of an implanted graft, particularly a vascular graft.

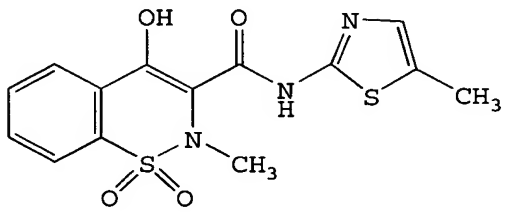
[078] The term "vaso-occlusive event" includes a partial occlusion (including a narrowing) or complete occlusion of a blood vessel, a stent or a vascular graft. A vaso-occlusive event, as used herein, expressly excludes an occlusion or event resulting from heart disease, as the term is defined herein.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[079] The present invention provides a combination therapy comprising the administration to a subject of a therapeutically effective amount of a COX-2 selective inhibitor in combination with a therapeutically effective amount of a calcium modulating agent. The combination therapy is used to treat or prevent a vaso-occlusive event, to inhibit inflammation in the vessels, and to treat or prevent disorders associated with vaso-occlusions. When administered as part of a combination therapy, the COX-2 selective inhibitor together with the calcium modulating agent provide enhanced treatment options as compared to administration of either the calcium modulating agent or the COX-2 selective inhibitor alone.

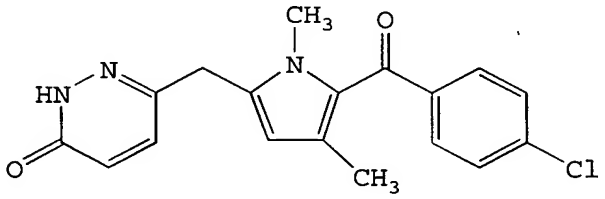
CYCLOOXYGENASE-2 SELECTIVE INHIBITORS

[080] A number of suitable cyclooxygenase-2 selective inhibitors or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof may be employed in the composition of the current invention. In one embodiment, the cyclooxygenase-2 selective inhibitor can be, for example, the cyclooxygenase-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-1.



B-1

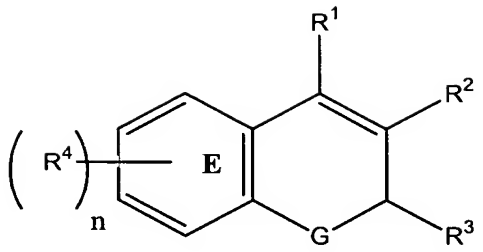
[081] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is the cyclooxygenase-2 selective inhibitor, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-2.



B-2

[082] In still another embodiment the cyclooxygenase-2 selective inhibitor is a chromene compound that is a substituted benzopyran or a substituted benzopyran analog, and even more typically, selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, dihydronaphthalenes or a compound having Formula *I* shown below and possessing, by way of example and not limitation, the structures disclosed in Table 1x. Furthermore, benzopyran cyclooxygenase-2 selective inhibitors useful in the practice of the present methods are described in U.S. Patent No. 6,034,256 and 6,077,850 herein incorporated by reference in their entirety.

[083] In another embodiment, the cyclooxygenase-2 selective inhibitor is a chromene compound represented by Formula *I* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(I)

[084] wherein:

[085] n is an integer which is 0, 1, 2, 3 or 4;

[086] G is O, S or NR^a;

[087] R^a is alkyl;

[088] R^1 is selected from the group consisting of H and aryl;

[089] R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[090] R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

[091] each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

[092] or R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[093] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[094] n is an integer which is 0, 1, 2, 3 or 4;

[095] G is O, S or NR^a;

[096] R^1 is H;

[097] R^a is alkyl;

[098] R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[099] R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

[0100] each R^4 is independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^4 together with ring E forms a naphthyl radical.

[0101] In a further embodiment, the cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)*, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[0102] n is an integer which is 0, 1, 2, 3 or 4;

[0103] G is oxygen or sulfur;

[0104] R^1 is H;

[0105] R^2 is carboxyl, lower alkyl, lower aralkyl or lower alkoxycarbonyl;

[0106] R^3 is lower haloalkyl, lower cycloalkyl or phenyl; and

[0107] each R^4 is H, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or

[0108] R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0109] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[0110] R^2 is carboxyl;

[0111] R^3 is lower haloalkyl; and

[0112] each R^4 is H, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or wherein R^4 together with ring E forms a naphthyl radical.

[0113] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[0114] n is an integer which is 0, 1, 2, 3 or 4;

[0115] R^3 is fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, or trifluoromethyl; and

[0116] each R^4 is H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl or phenyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0117] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[0118] n is an integer which is 0, 1, 2, 3 or 4;

[0119] R^3 is trifluoromethyl or pentafluoroethyl; and

[0120] each R^4 is independently H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl,

methylsulfonyl, benzylcarbonyl, or phenyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0121] In yet another embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound having the structure of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[0122] n = 4;

[0123] G is O or S;

[0124] R^1 is H;

[0125] R^2 is CO_2H;

[0126] R^3 is lower haloalkyl;

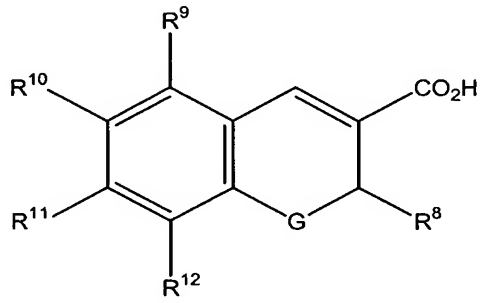
[0127] a first R^4 corresponding to R^9 is hydrido or halo;

[0128] a second R^4 corresponding to R^{10} is H, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, or 6- membered nitrogen-containing heterocyclosulfonyl;

[0129] a third R^4 corresponding to R^{11} is H, lower alkyl, halo, lower alkoxy, or aryl; and

[0130] a fourth R^4 corresponding to R^{12} is H, halo, lower alkyl, lower alkoxy, and aryl;

[0131] wherein Formula *(I)* is represented by Formula *(Ia)*:



(Ia)

[0132] The cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound of having the structure of Formula *(Ia)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[0133] R^8 is trifluoromethyl or pentafluoroethyl;

[0134] R^9 is H, chloro, or fluoro;

[0135] R^{10} is H, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, or morpholinosulfonyl;

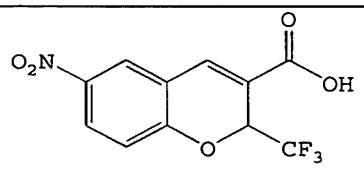
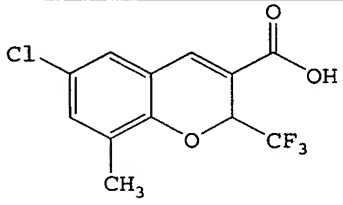
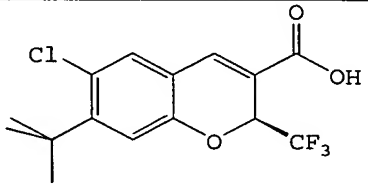
[0136] R^{11} is H, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, or phenyl; and

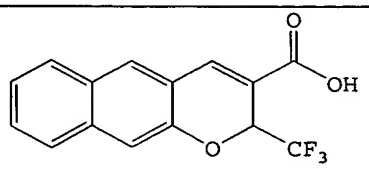
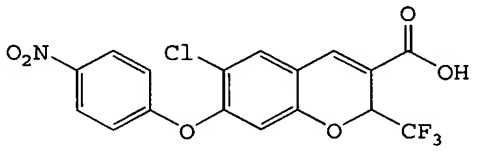
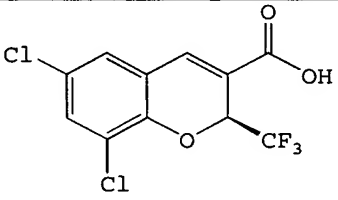
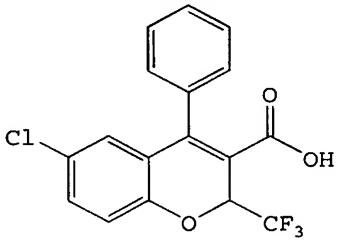
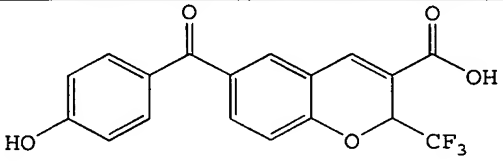
[0137] R^{12} is H, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, or phenyl.

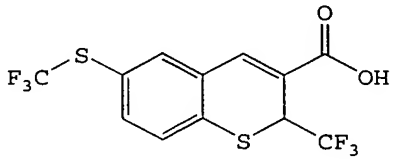
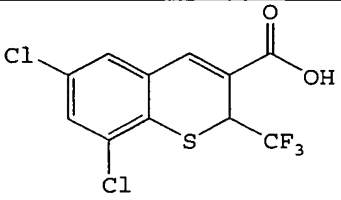
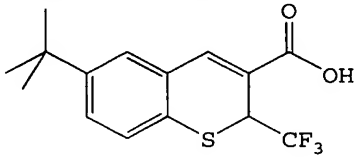
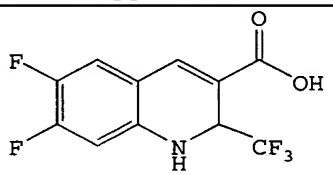
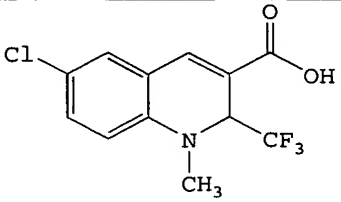
[0138] Examples of exemplary chromene cyclooxygenase-2 selective inhibitors are depicted in Table 1x below.

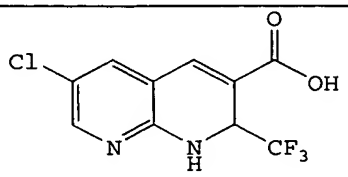
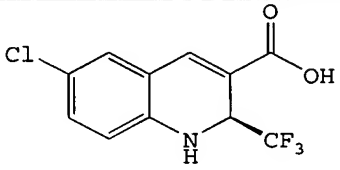
TABLE 1X

EXAMPLES OF CHROMENE CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

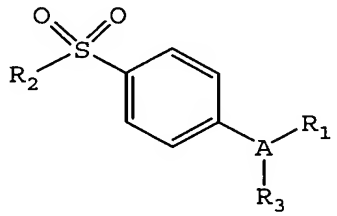
Compound Number	**Structural Formula**
B-3	 6-Nitro-2-trifluoromethyl-2H-1 -benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl) -2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

[0139] In a further embodiment, the cyclooxygenase-2 selective inhibitor is selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of Formula *I*: or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:



II

[0140] A is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

[0141] R_1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R_1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

[0142] R_2 is selected from the group consisting of methyl or amino; and

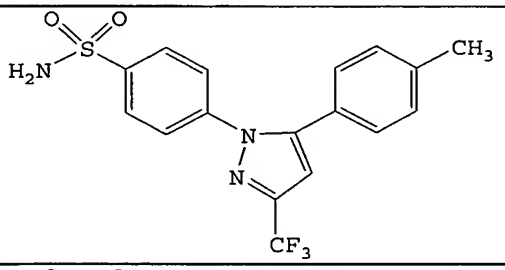
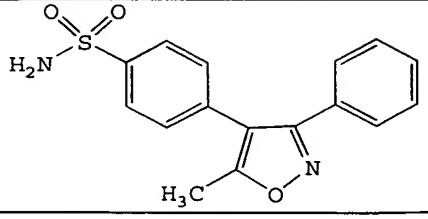
[0143] R_3 is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy,

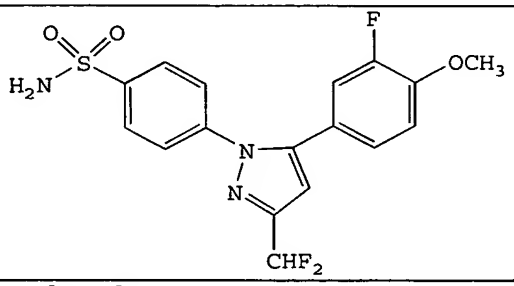
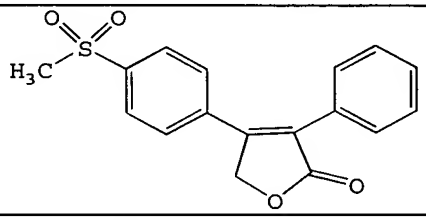
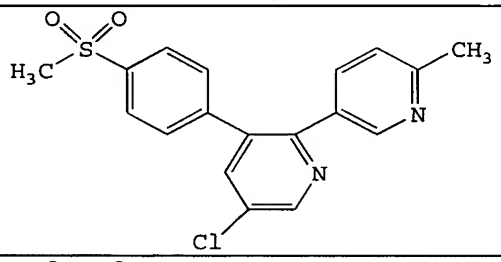
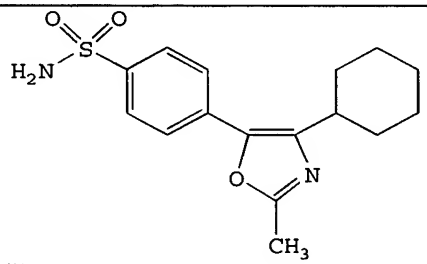
alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl.

[0144] In another embodiment, the cyclooxygenase-2 selective inhibitor represented by the above Formula *II* is selected from the group of compounds illustrated in Table 2x, consisting of celecoxib (B-18; U.S. Patent No. 5,466,823; CAS No. 169590-42-5), valdecoxib (B-19; U.S. Patent No. 5,633,272; CAS No. 181695-72-7), deracoxib (B-20; U.S. Patent No. 5,521,207; CAS No. 169590-41-4), rofecoxib (B-21; CAS No. 162011-90-7), etoricoxib (MK-663; B-22; PCT publication WO 98/03484), tilmacoxib (JTE-522; B-23; CAS No. 180200-68-4).

TABLE 2X

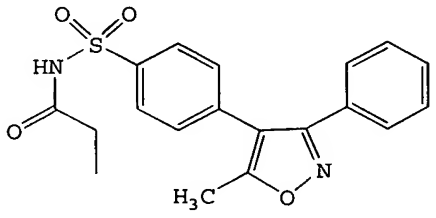
EXAMPLES OF TRICYCLIC CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

Compound Number	**Structural Formula**
B-18	
B-19	

Compound Number	Structural Formula
B-20	
B-21	
B-22	
B-23	

[0145] In still another embodiment, the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

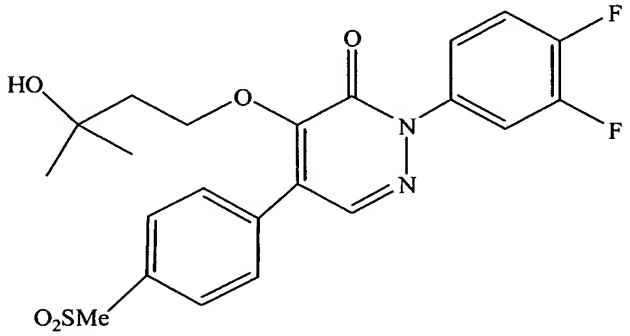
[0146] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is parecoxib (B-24, U.S. Patent No. 5,932,598, CAS No. 198470-84-7), which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, may be advantageously employed as a source of a cyclooxygenase inhibitor (US 5,932,598, herein incorporated by reference).



B-24

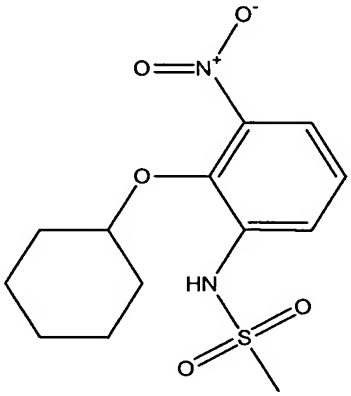
[0147] One form of parecoxib is sodium parecoxib.

[0148] In another embodiment of the invention, the compound having the formula B-25 or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-25 that has been previously described in International Publication number WO 00/24719 (which is herein incorporated by reference) is another tricyclic cyclooxygenase-2 selective inhibitor that may be advantageously employed.



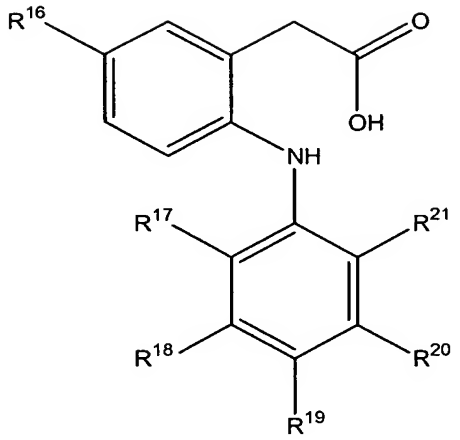
B-25

[0149] Another cyclooxygenase-2 selective inhibitor that is useful in connection with the method(s) of the present invention is N-(2-cyclohexyloxynitrophenyl)-methane sulfonamide (NS-398) having a structure shown below as B-26, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-26.



B-26

[0150] In yet a further embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula *(III)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(III)

[0151] wherein:

R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro;

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro; and

R^{21} is chloro, fluoro, trifluoromethyl or methyl, provided that R^{17}, R^{18}, R^{19} and R^{20} are not all fluoro when R^{16} is ethyl and R^{19} is H.

[0152] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention is a compound that has the designation of COX 189 (lumiracoxib; B-211) and that has the structure shown in Formula *(III)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

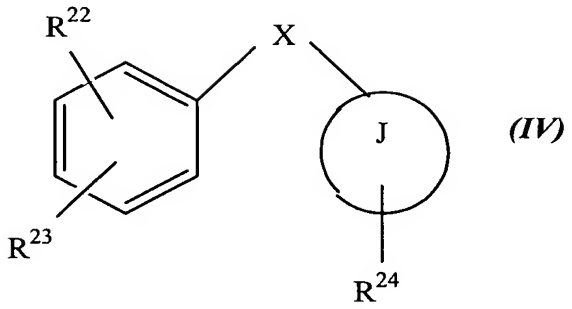
R^{16} is ethyl;

R^{17} and R^{19} are chloro;

R^{18} and R^{20} are hydrogen; and

and R^{21} is methyl.

[0153] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is represented by Formula *(IV)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(IV)

[0154] wherein:

X is O or S;

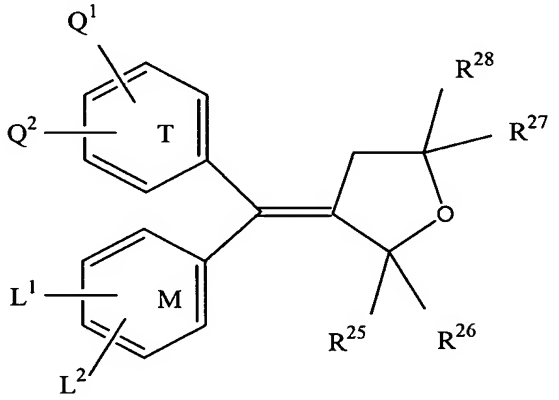
J is a carbocycle or a heterocycle;

R^{22} is $NHSO_2CH_3$ or F;

R^{23} is H, NO_2, or F; and

R^{24} is H, $NHSO_2CH_3$, or $(SO_2CH_3)C_6H_4$.

[0155] According to another embodiment, the cyclooxygenase-2 selective inhibitors used in the present method(s) have the structural Formula *(V)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(V)

[0156] wherein:

T and M independently are phenyl, naphthyl, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

Q^1, Q^2, L^1 or L^2 are independently hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, trifluoromethyl, or lower methoxy having from 1 to 6 carbon atoms; and

at least one of Q^1, Q^2, L^1 or L^2 is in the para position and is $-S(O)_n-R$, wherein n is 0, 1, or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms or a lower haloalkyl radical having from 1 to 6 carbon atoms, or an $-SO_2NH_2$; or,

^{1} and Q^2 are methylenedioxy; or

L^1 and L^2 are methylenedioxy; and

R^{25}, R^{26}, R^{27}, and R^{28} are independently hydrogen, halogen, lower alkyl radical having from 1 to 6 carbon atoms, lower haloalkyl radical having from 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{25} and R^{26} are O; or,

R^{27} and R^{28} are O; or,

R^{25}, R^{26}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms; or,

R^{27}, R^{28}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms.

[0157] In another embodiment, the compounds N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof having the structure of Formula *(V)* are employed as cyclooxygenase-2 selective inhibitors.

[0158] In a further embodiment, compounds that are useful for the cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof used in connection with the method(s) of the present invention, the structures for which are set forth in Table 3x below, include, but are not limited to:

[0159] 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-27);

[0160] 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-28);

[0161] 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-29);

[0162] 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-30);

[0163] 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid (B-31);

[0164] 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-32);

[0165] 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-33);

[0166] 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-34);

[0167] 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-35);

[0168] 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-36);

[0169] 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-37);

[0170] 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-38);

[0171] 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-39);

[0172] 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-40);

[0173] 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-41);

[0174] 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-42);

[0175] 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-43);

[0176] 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-44);

[0177] 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-45);

[0178] 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-46);

[0179] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-47);

[0180] 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-48)

[0181] 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-49);

[0182] 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-50);

[0183] 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-51);

[0184] 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-52);

[0185] 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-53);

[0186] 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-54);

[0187] 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-55);

[0188] 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-56);

[0189] 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-57);

[0190] 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-58);

[0191] 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-59);

[0192] 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-60);

[0193] 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-61);

[0194] 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-62);

[0195] 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-63);

[0196] 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-64);

[0197] 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-65);

[0198] 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-66);

[0199] 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-67);

[0200] 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-68);

[0201] 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-69);

[0202] 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-70);

[0203] 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-71);

[0204] 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid (B-72);

[0205] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-73);

[0206] 3-[(3-Chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one or BMS-347070 (B-74);

[0207] 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine (B-75);

[0208] 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone (B-76);

[0209] 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (B-77);

[0210] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole (B-78);

[0211] 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-79);

[0212] 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-80);

[0213] 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-81);

[0214] 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-82);

[0215] 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-83);

[0216] 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-84);

[0217] 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-85);

[0218] 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-86);

[0219] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-87);

[0220] 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-88);

[0221] 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-89);

[0222] 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-90);

[0223] 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-91);

[0224] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-92);

[0225] 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-93);

[0226] 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-94);

[0227] 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide (B-95);

[0228] 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-96);

[0229] 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-97);

[0230] 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-98);

[0231] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-99);

[0232] 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide (B-100);

[0233] 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-101);

[0234] 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-102);

[0235] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-103);

[0236] 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-104);

[0237] 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene (B-105);

[0238] 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-106);

[0239] 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-107);

[0240] 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-108);

[0241] 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-109);

[0242] 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-110);

[0243] 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (B-111);

[0244] 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (B-112);

[0245] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole (B-113);

[0246] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-114);

[0247] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole (B-115);

[0248] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole (B-116);

[0249] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole (B-117);

[0250] 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole (B-118);

[0251] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-119);

[0252] 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene (B-120);

[0253] 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide (B-121);

[0254] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene (B-122);

[0255] 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide (B-123);

[0256] 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-124);

[0257] 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-125);

[0258] 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile (B-126);

[0259] 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-127);

[0260] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-128);

[0261] 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-129);

[0262] 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-130);

[0263] 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-131);

[0264] 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-132);

[0265] 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-133);

[0266] 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-134);

[0267] 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-135);

[0268] 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-136);

[0269] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole (B-137);

[0270] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole (B-138);

[0271] 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (B-139);

[0272] 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole (B-140);

[0273] 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole (B-141);

[0274] 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-142);

[0275] 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-143);

[0276] 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-144);

[0277] 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-145);

[0278] 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-146);

[0279] 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-147);

[0280] 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole (B-148);

[0281] 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-149);

[0282] 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-150);

[0283] 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-151);

[0284] 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-152);

[0285] 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide (B-153);

[0286] N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide (B-154);

[0287] ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate (B-155);

[0288] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole (B-156);

[0289] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole (B-157);

[0290] 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-158);

[0291] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole (B-159);

[0292] 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole (B-160);

[0293] 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-161);

[0294] 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-162);

[0295] 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine (B-163);

[0296] 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-164);

[0297] 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide (B-165);

[0298] 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene (B-166);

[0299] 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole (B-167);

[0300] 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide (B-168);

[0301] 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-169);

[0302] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-170);

[0303] 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide (B-171);

[0304] 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-172);

[0305] 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-173);

[0306] 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-174);

[0307] 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-175);

[0308] 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-176);

[0309] 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-177);

[0310] 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-178);

[0311] 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide (B-179);

[0312] 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-180);

[0313] 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide (B-181);

[0314] 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-182);

[0315] 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-183);

[0316] 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-184);

[0317] 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-185);

[0318] 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide (B-186);

[0319] 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-187);

[0320] 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-188);

[0321] 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide (B-189);

[0322] ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate (B-190);

[0323] 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid (B-191);

[0324] 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole (B-192);

[0325] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole (B-193);

[0326] 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole (B-194);

[0327] 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (B-195);

[0328] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-196);

[0329] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-197);

[0330] 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone (B-198);

[0331] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-199);

[0332] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-200);

[0333] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-201);

[0334] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-202);

[0335] 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-203);

[0336] 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-204);

[0337] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-205);

[0338] 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-206);

[0339] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-207);

[0340] [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide (B-208);

[0341] 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide (B-209);

[0342] 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (B-210);

[0343] [2-(2-chloro-6-fluoro-phenylamino)-5-methyl-phenyl]-acetic acid or COX 189 (lumiracoxib; B-211);

[0344] N-(4-Nitro-2-phenoxy-phenyl)-methanesulfonamide or nimesulide (B-212);

[0345] N-[6-(2,4-difluoro-phenoxy)-1-oxo-indan-5-yl]-methanesulfonamide or flosulide (B-213);

[0346] N-[6-(2,4-Difluoro-phenylsulfanyl)-1-oxo-1H-inden-5-yl]-methanesulfonamide, soldium salt or L-745337 (B-214);

[0347] N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide or RWJ-63556 (B-215);

[0348] 3-(3,4-Difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl-5-(2,2,2-trifluoro-ethyl)-5H-furan-2-one or L-784512 or L-784512 (B-216);

[0349] (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4(5H)-thiazolone or darbufelone (B-217);

[0350] CS-502 (B-218);

[0351] LAS-34475 (B-219);

[0352] LAS-34555 (B-220);

[0353] S-33516 (B-221);

[0354] SD-8381 (B-222);

[0355] L-783003 (B-223);

[0356] N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide or T-614 (B-224);

[0357] D-1367 (B-225);

[0358] L-748731 (B-226);

[0359] (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid or CT3 (B-227);

[0360] CGP-28238 (B-228);

[0361] 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389 (B-229);

[0362] GR-253035 (B-230);

[0363] 6-dioxo-9H-purin-8-yl-cinnamic acid (B-231);

[0364] S-2474 (B-232);

[0365] 4-[4-(methyl)-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone;

[0366] 4-(5-methyl-3-phenyl-4-isoxazolyl);

[0367] 2-(6-methylpyrid-3-yl)-3-(4-methylsulfonylphenyl)-5-chloropyridine;

[0368] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl];

[0369] N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl];

[0370] 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

[0371] (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;

[0372] 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridzainone;

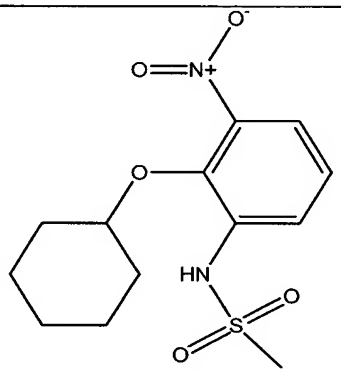
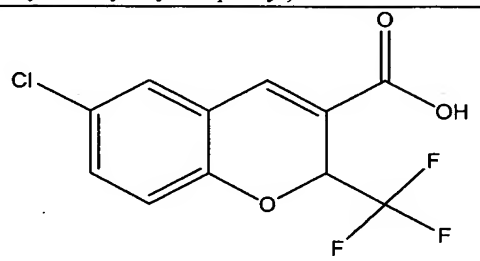
[0373] 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

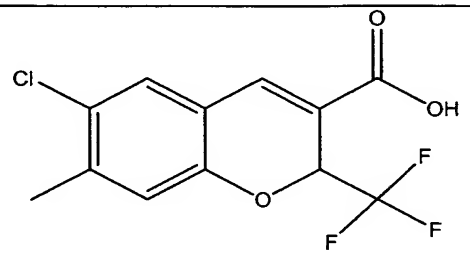
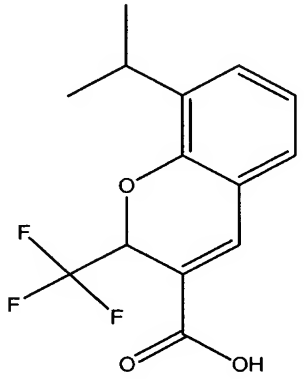
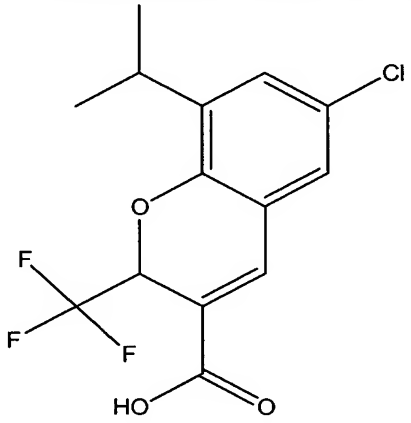
[0374] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

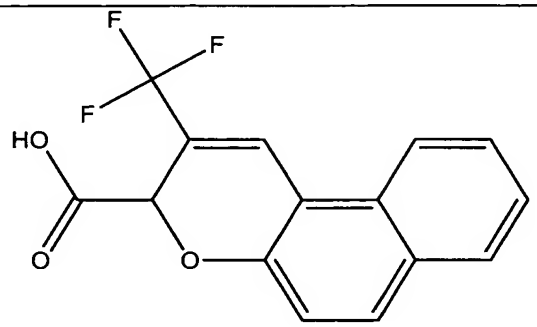
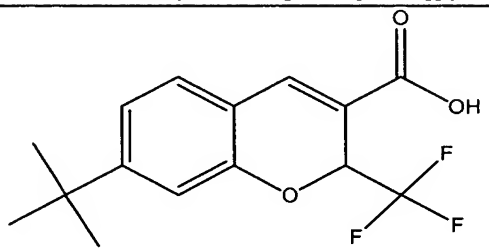
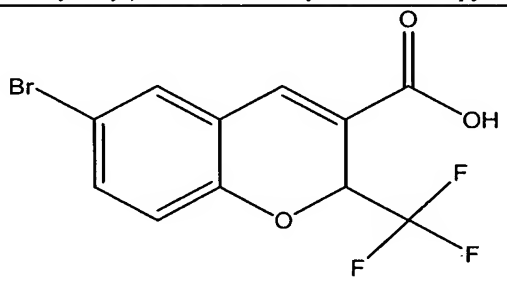
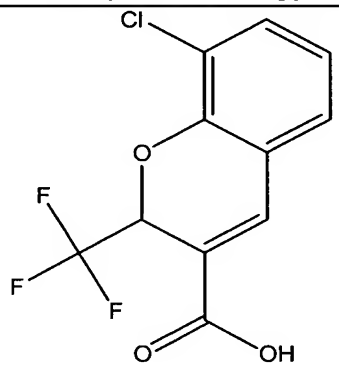
[0375] [2-(2,4-dichloro-6-ethyl-3,5-dimethyl-phenylamino)-5-propyl-phenyl]-acetic acid.

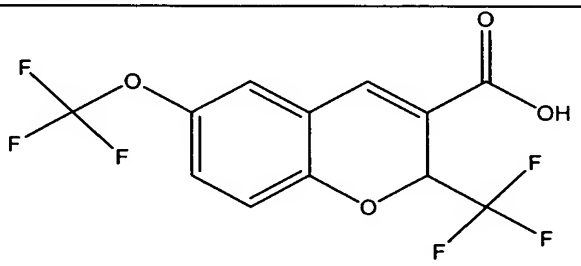
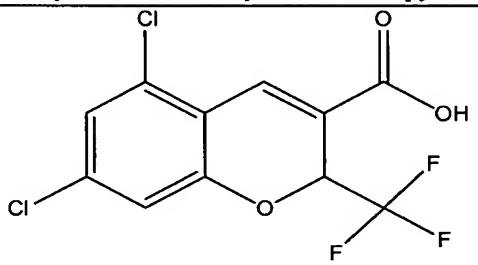
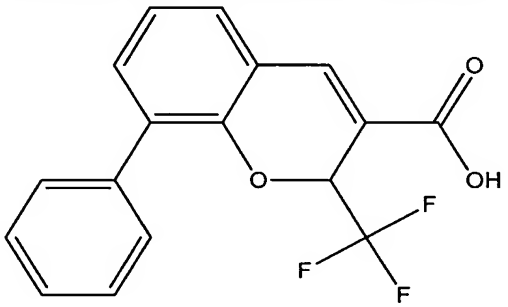
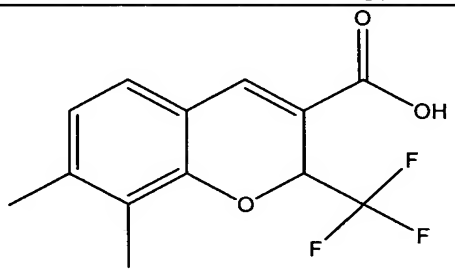
TABLE 3X

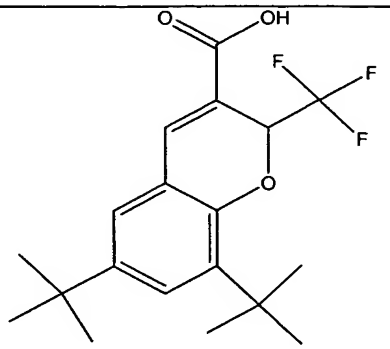
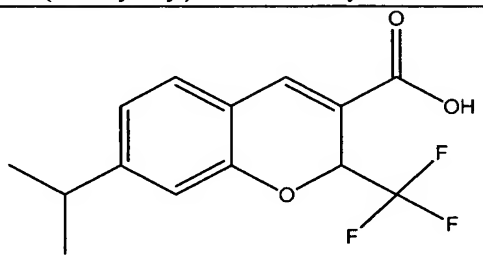
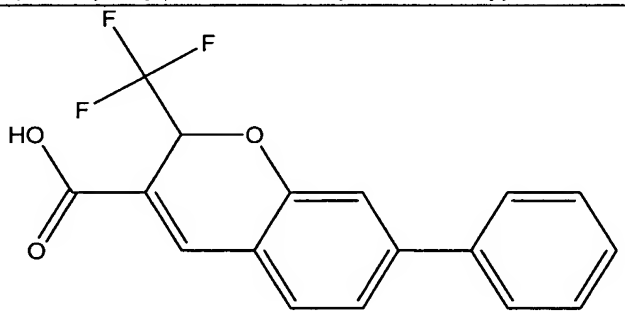
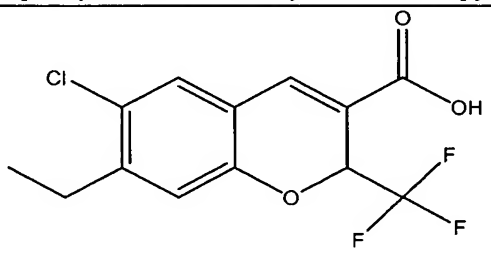
EXAMPLES OF CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

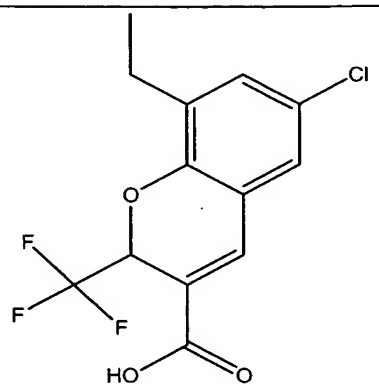
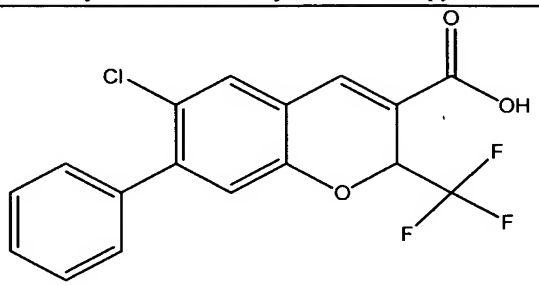
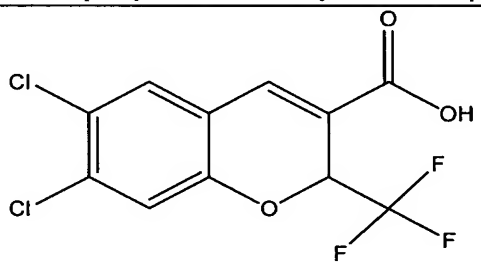
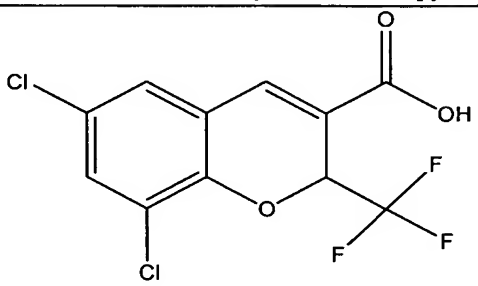
Compound Number	**Structural Formula**
B-26	 N-(2-cyclohexyloxynitrophenyl) methane sulfonamide or NS-398;
B-27	 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

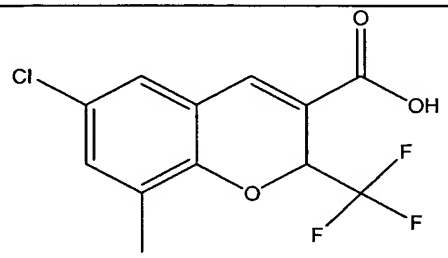
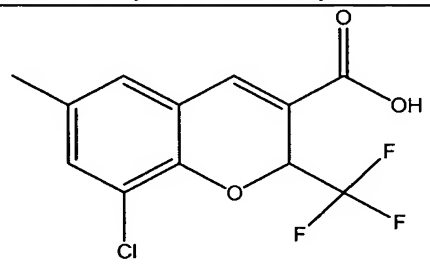
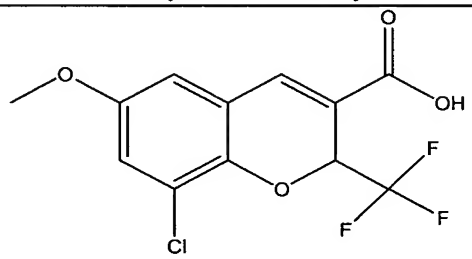
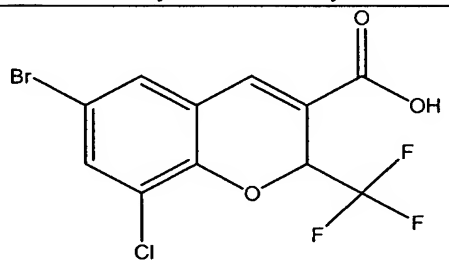
Compound Number	Structural Formula
B-28	 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-29	 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-30	 6-chloro-8-(1-methylethyl)-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;

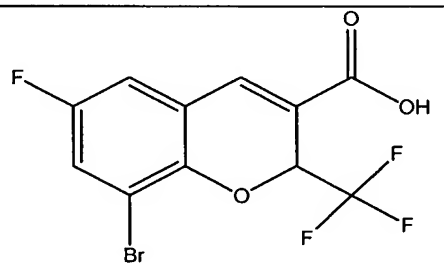
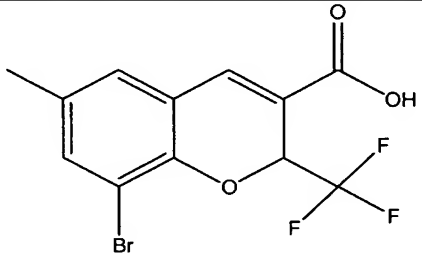
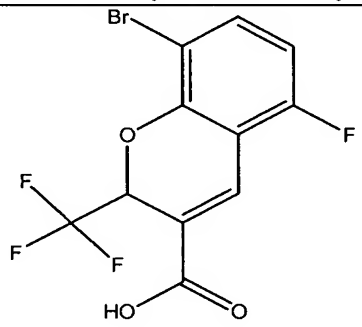
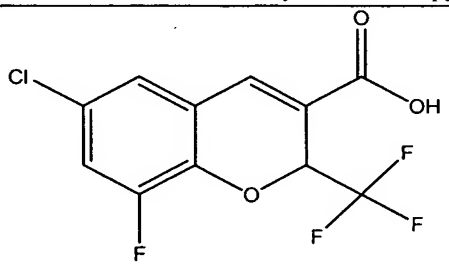
Compound Number	Structural Formula
B-31	 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;
B-32	 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-33	 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-34	 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

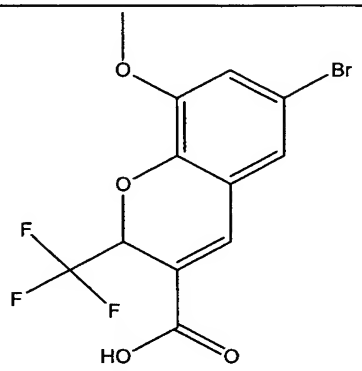
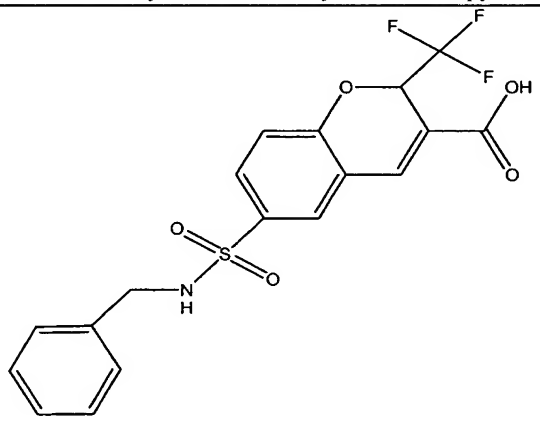
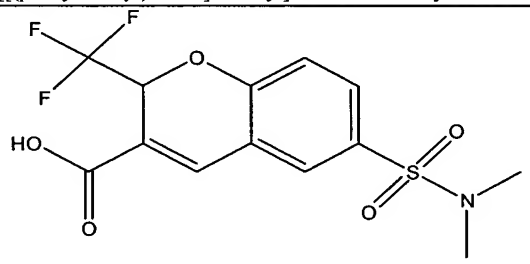
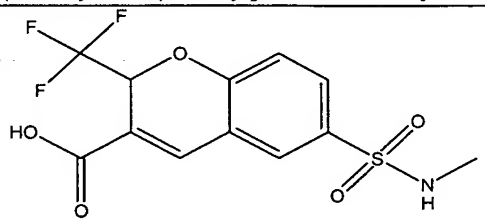
Compound Number	Structural Formula
B-35	 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-36	 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-37	 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-38	 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

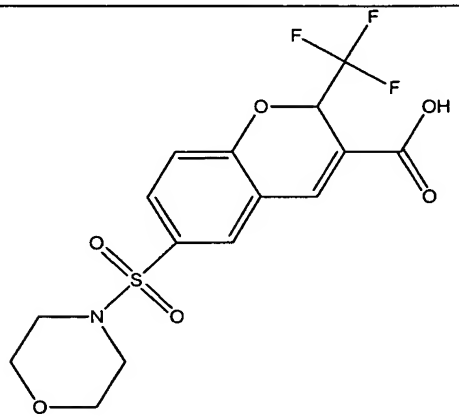
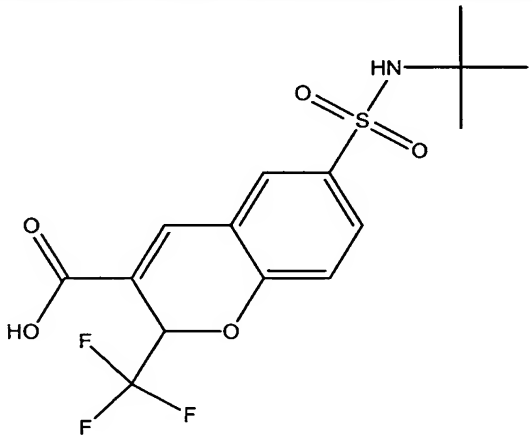
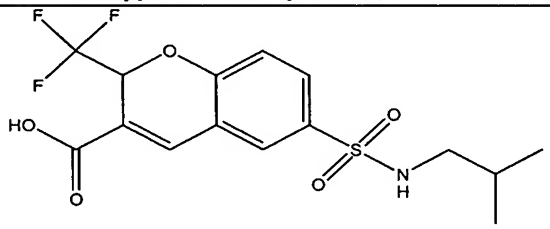
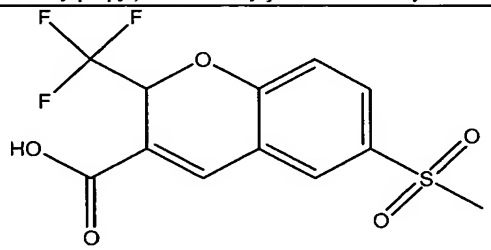
Compound Number	Structural Formula
B-39	 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-40	 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-41	 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-42	 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

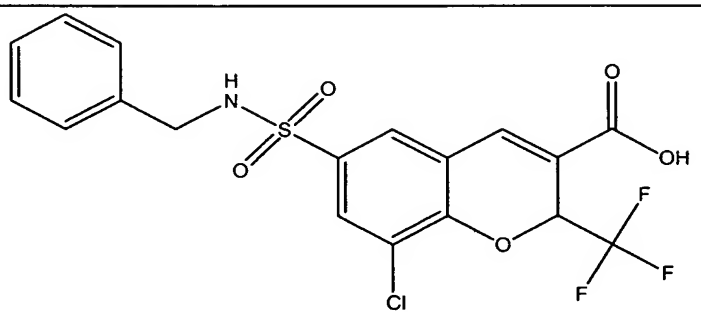
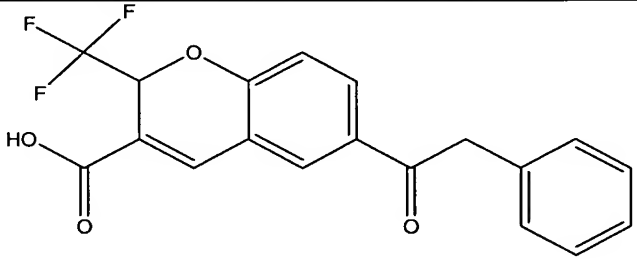
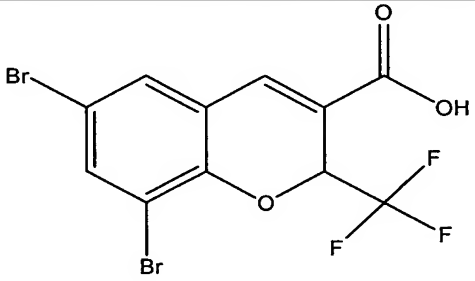
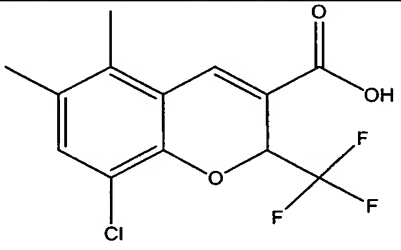
Compound Number	Structural Formula
B-43	 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-44	 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-45	 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-46	 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

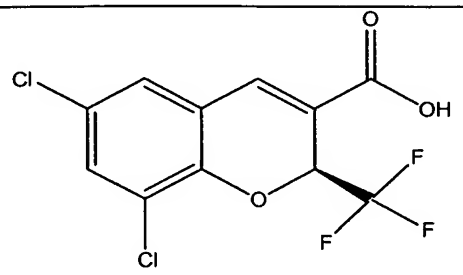
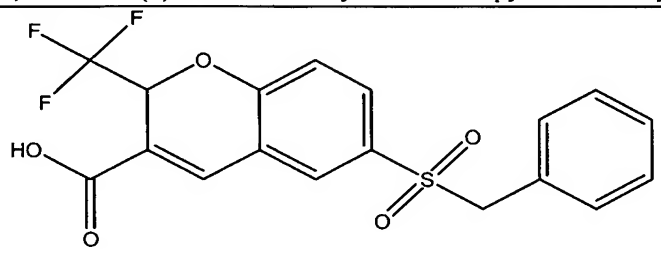
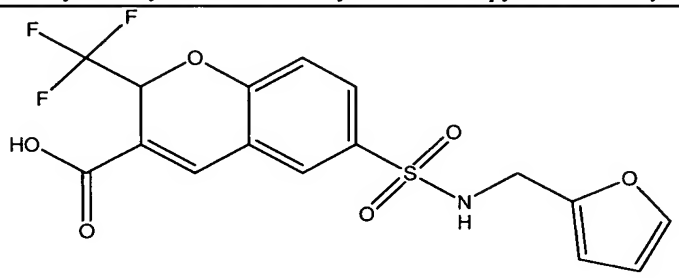
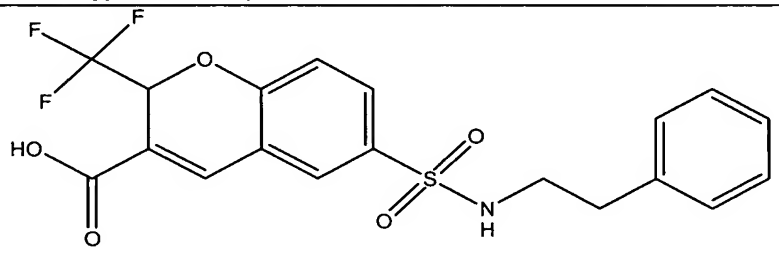
Compound Number	**Structural Formula**
B-47	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-48	 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-49	 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-50	 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

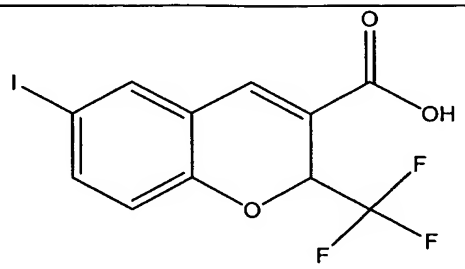
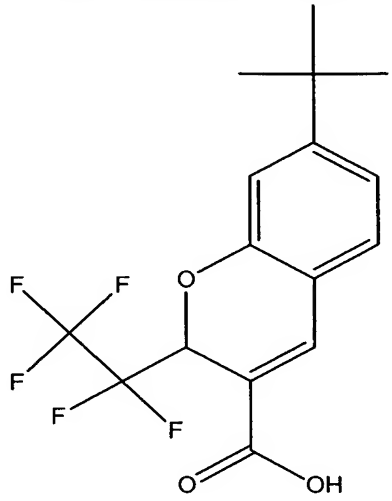
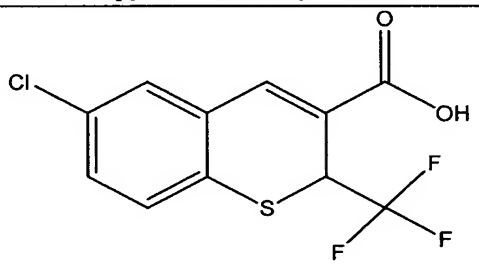
Compound Number	Structural Formula
B-51	 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-52	 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-53	 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-54	 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

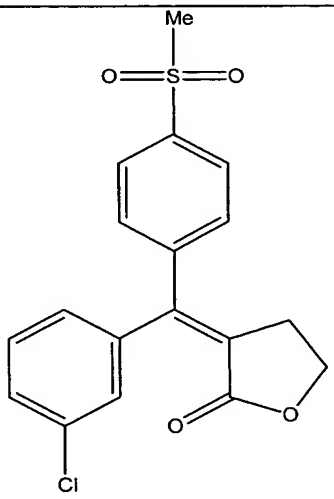
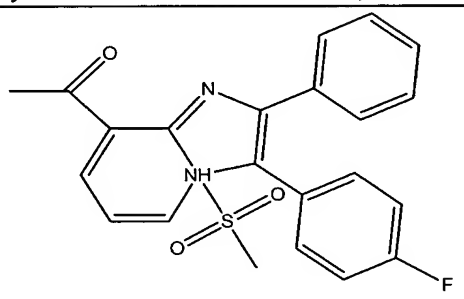
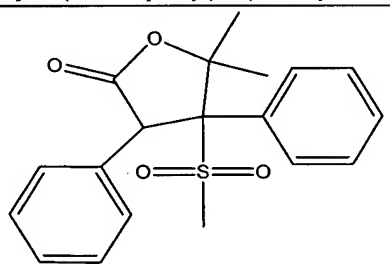
Compound Number	Structural Formula
B-55	 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-56	 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-57	 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-58	 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

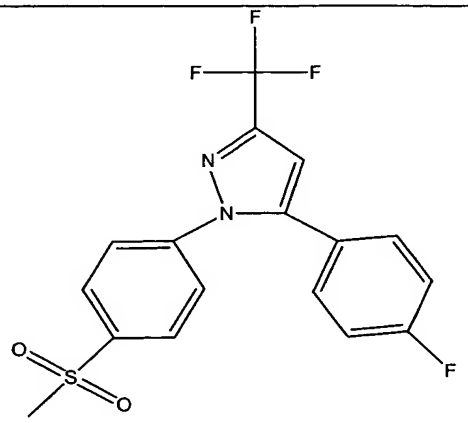
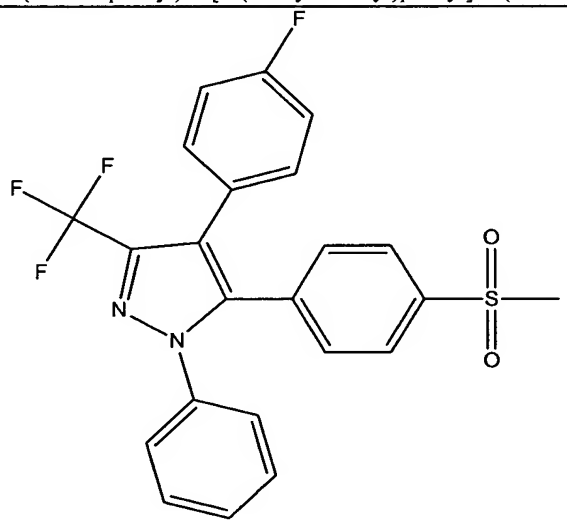
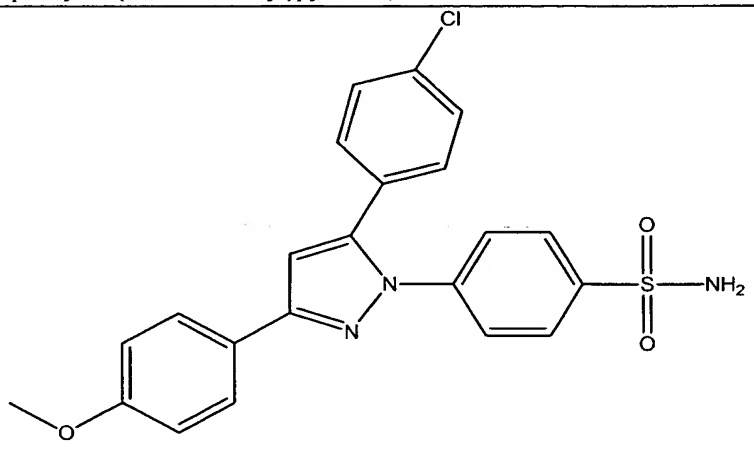
Compound Number	Structural Formula
B-59	 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-60	 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;
B-61	 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-62	 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

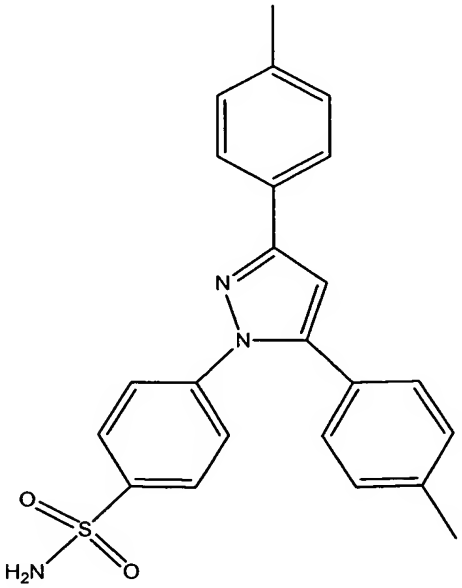
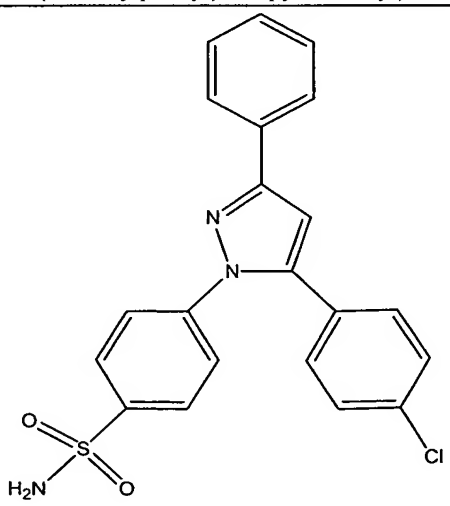
Compound Number	Structural Formula
B-63	 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-64	 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-65	 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-66	 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

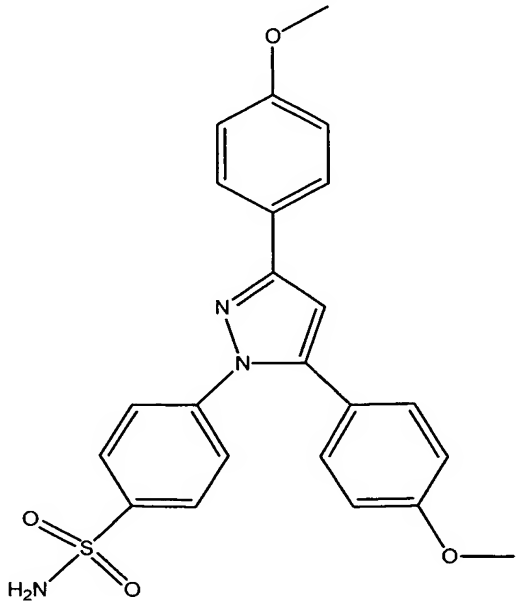
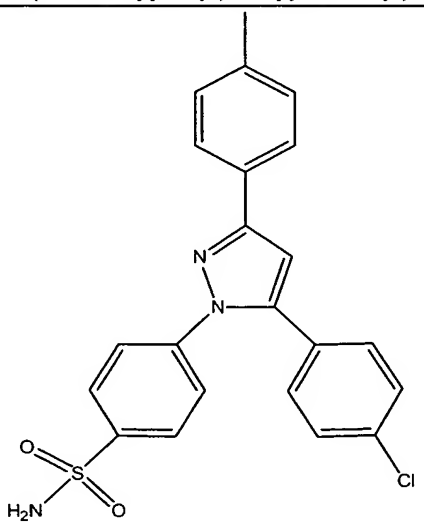
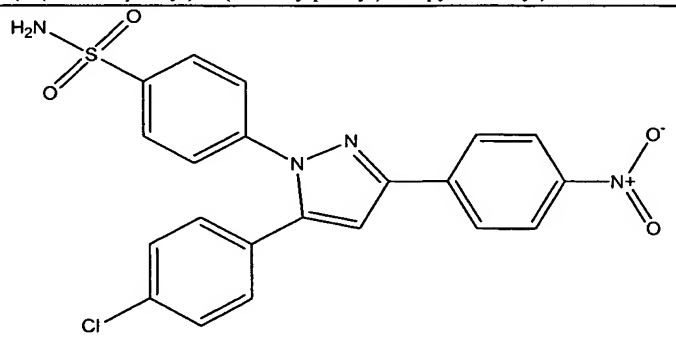
Compound Number	Structural Formula
B-67	 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-68	 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-69	 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;
B-70	 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran -3-carboxylic acid;

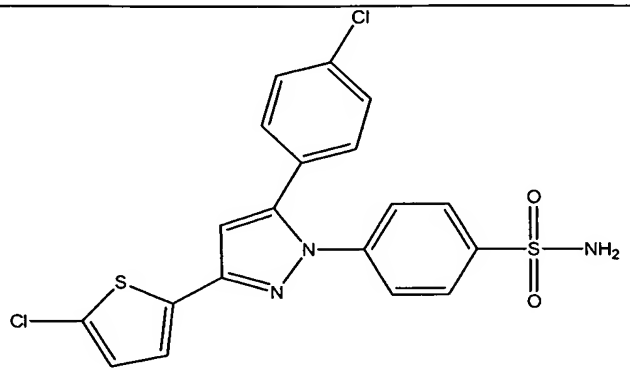
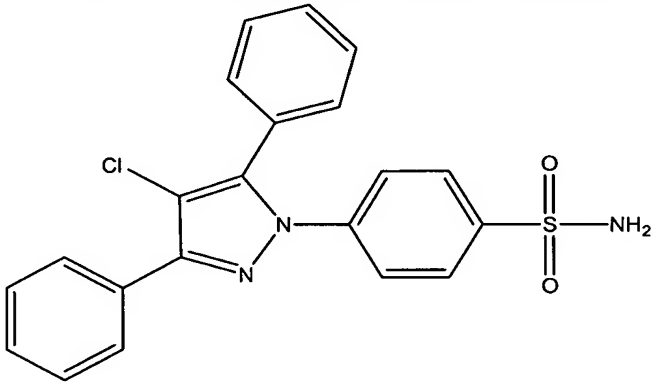
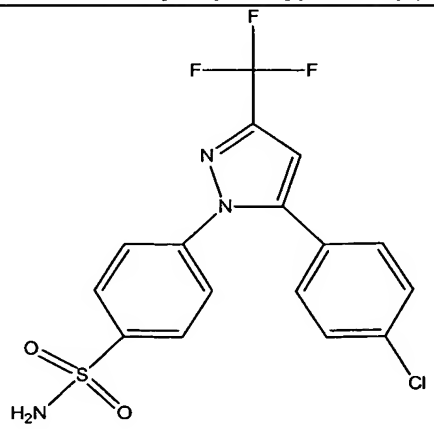
Compound Number	**Structural Formula**
B-71	 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-72	 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H -1-benzopyran-3-carboxylic acid;
B-73	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

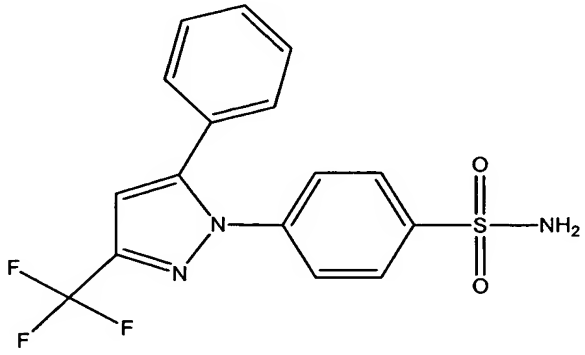
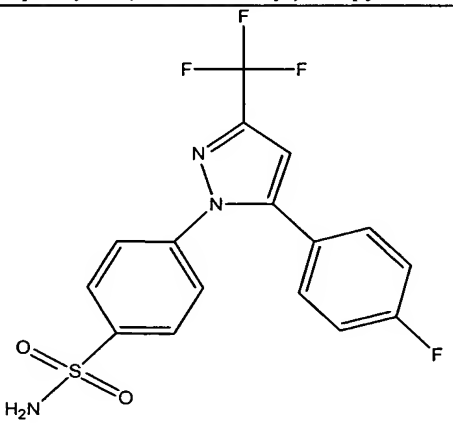
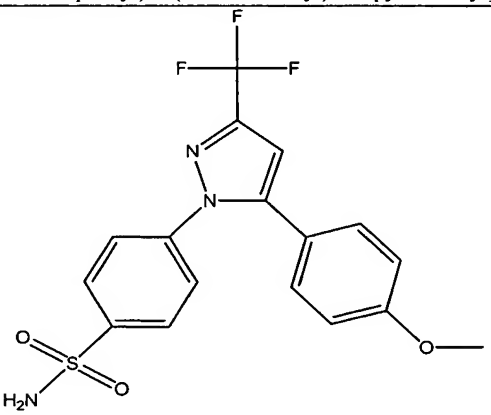
Compound Number	Structural Formula
B-74	 3-[(3-chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene] -dihydro-furan-2-one or BMS-347070;
B-75	 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;
B-76	 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

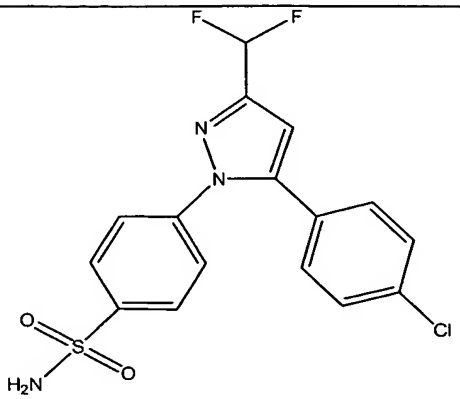
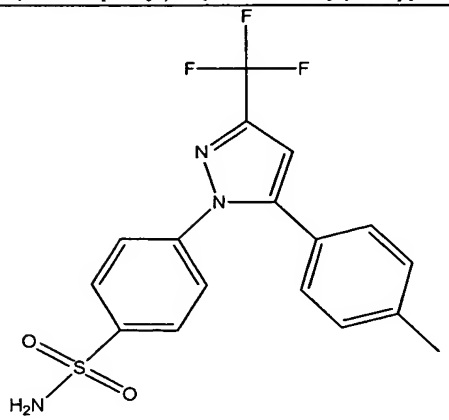
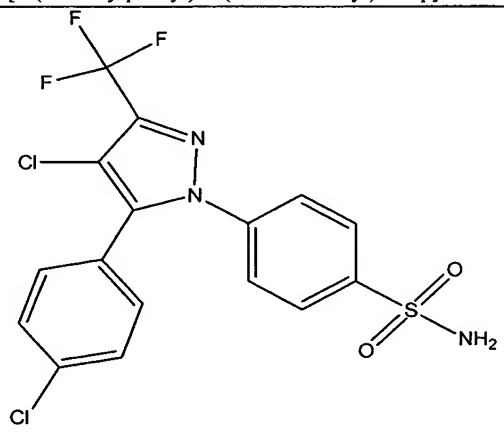
Compound Number	Structural Formula
B-77	 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;
B-78	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -1-phenyl-3-(trifluoromethyl)pyrazole;
B-79	 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide;

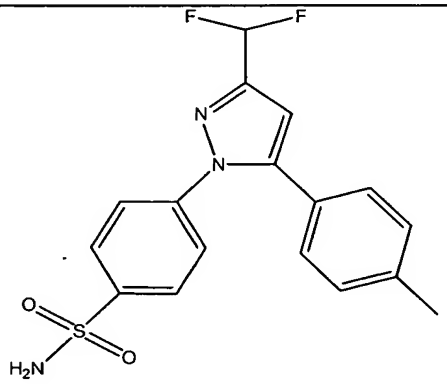
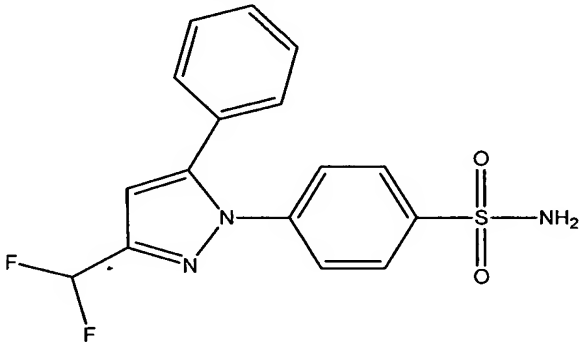
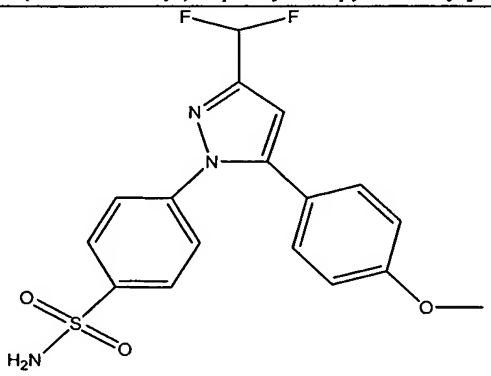
Compound Number	Structural Formula
B-80	 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-81	 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

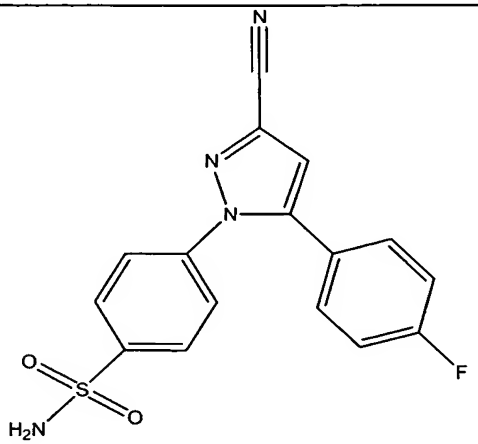
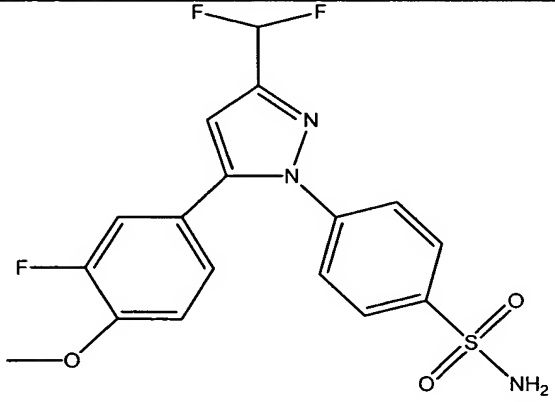
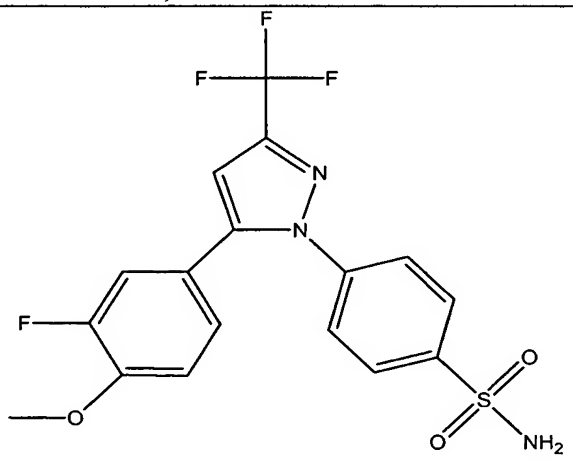
Compound Number	Structural Formula
B-82	 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-83	 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-84	 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

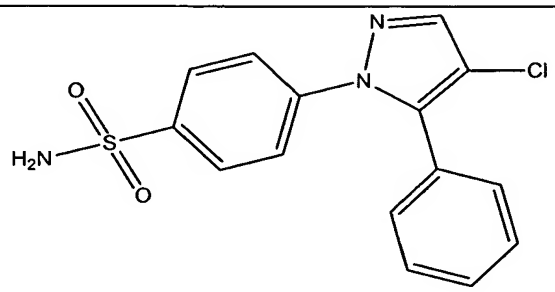
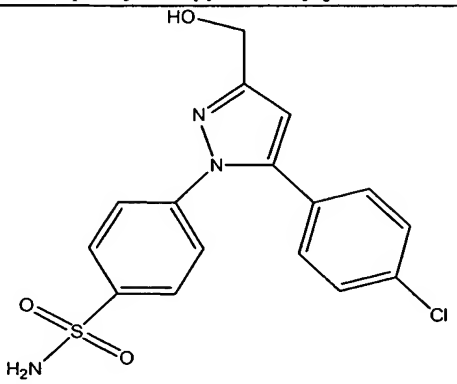
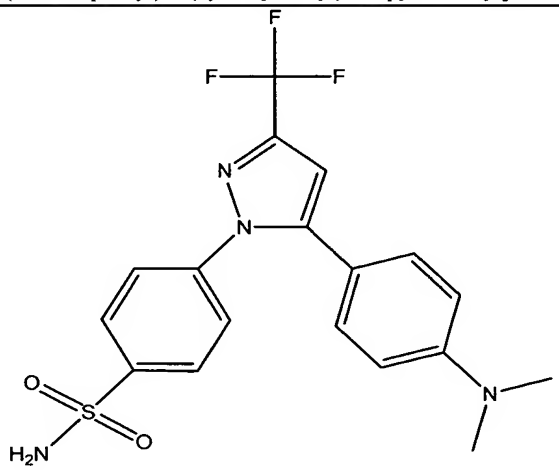
Compound Number	**Structural Formula**
B-85	 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-86	 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;
B-87	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

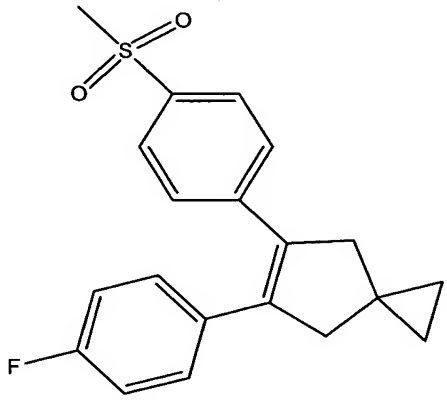
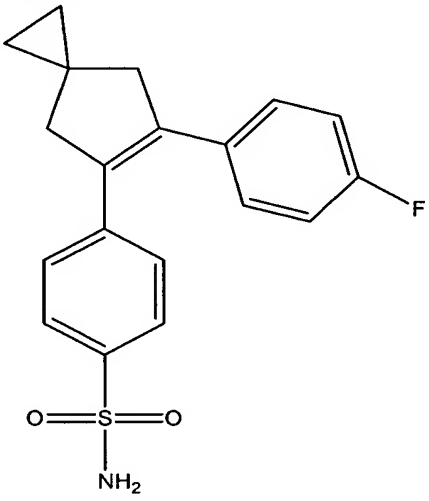
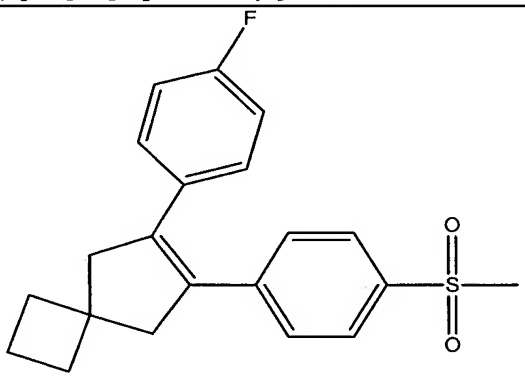
Compound Number	**Structural Formula**
B-88	 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-89	 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-90	 4[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

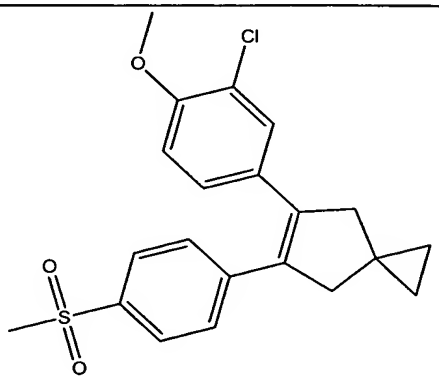
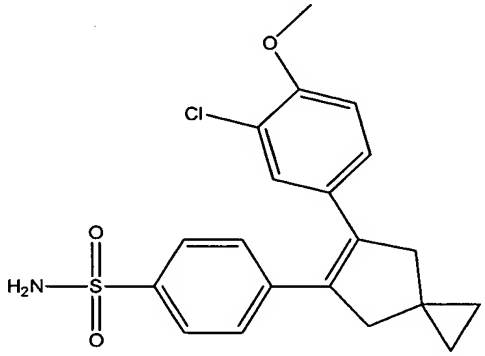
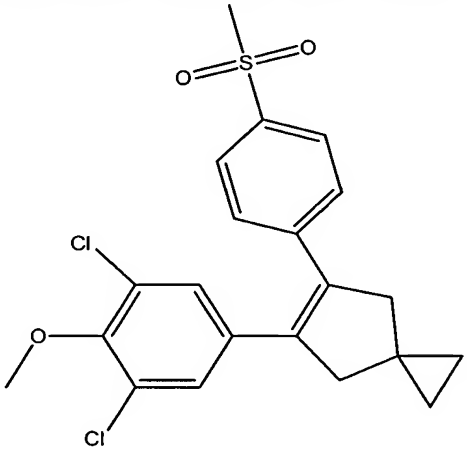
Compound Number	Structural Formula
B-91	 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-92	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-93	 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

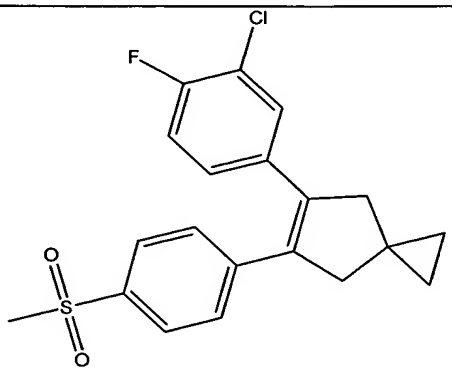
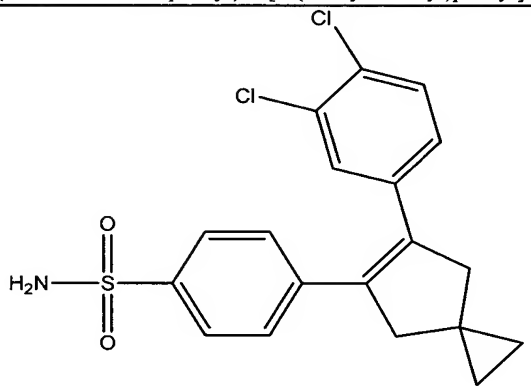
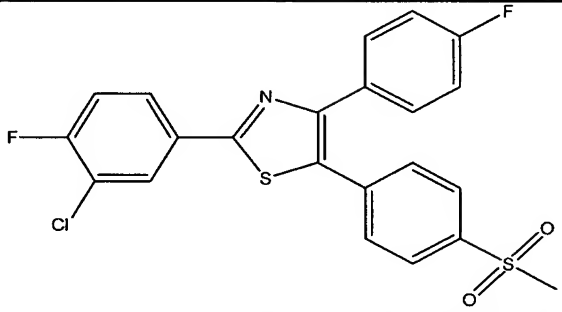
Compound Number	Structural Formula
B-94	 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-95	 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
B-96	 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

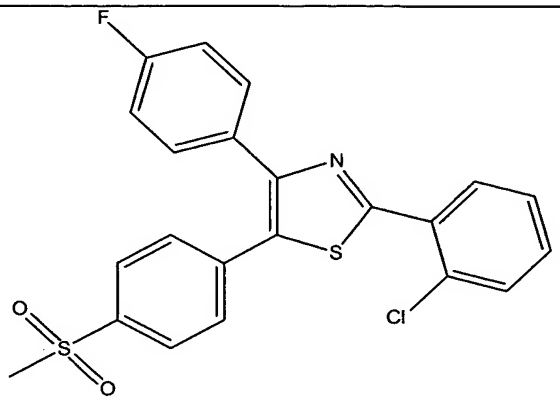
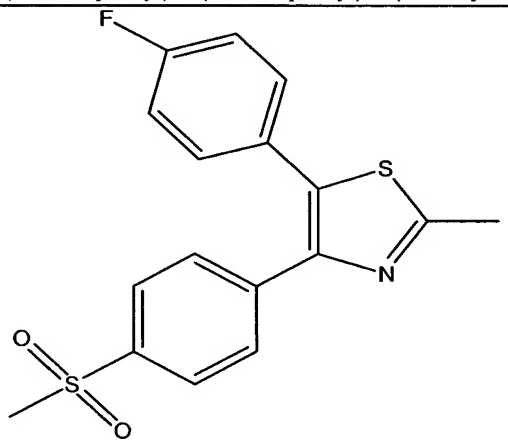
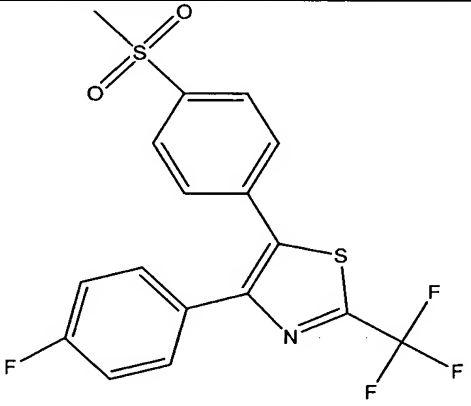
Compound Number	Structural Formula
B-97	 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-98	 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide;
B-99	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

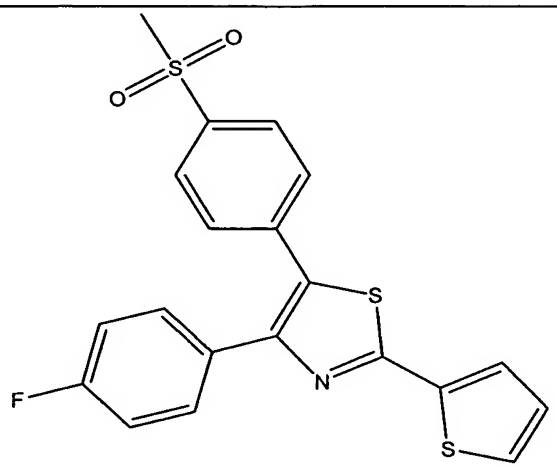
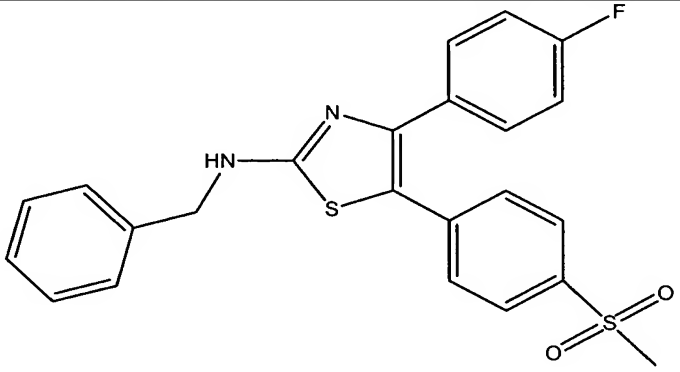
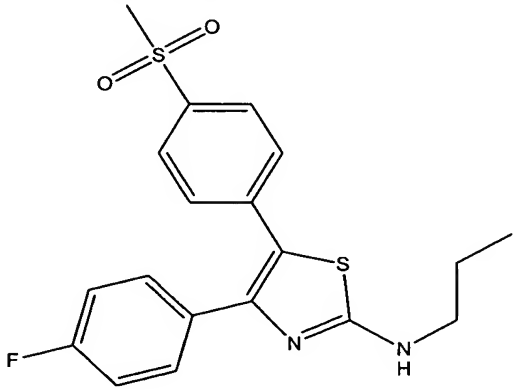
Compound Number	**Structural Formula**
B-100	 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
B-101	 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-102	 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide;

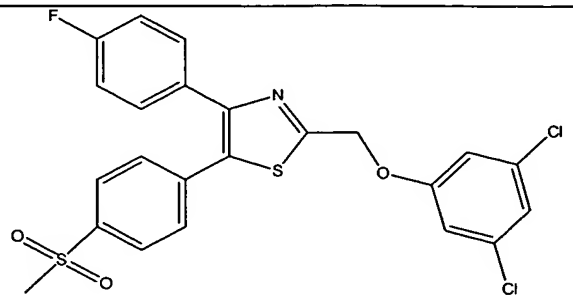
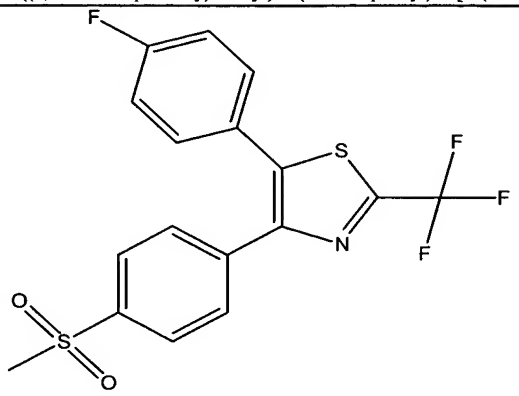
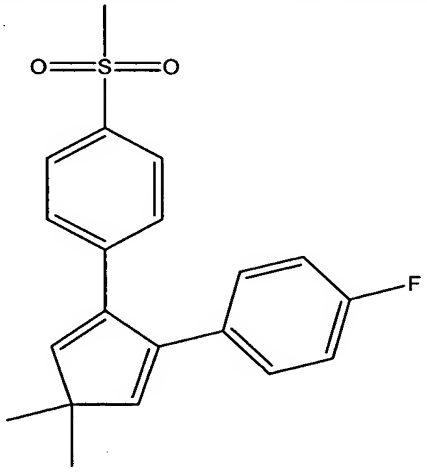
Compound Number	Structural Formula
B-103	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-104	 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-105	 6-(4-fluorophenyl)-7-[4-methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

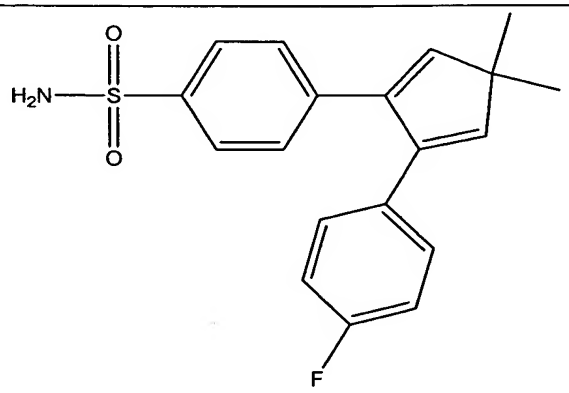
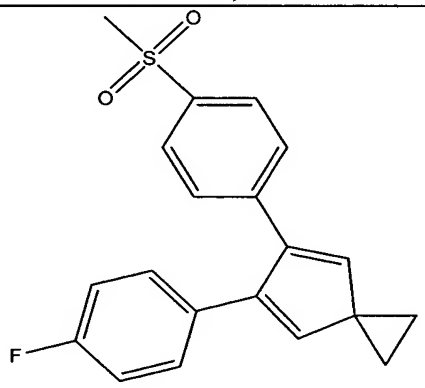
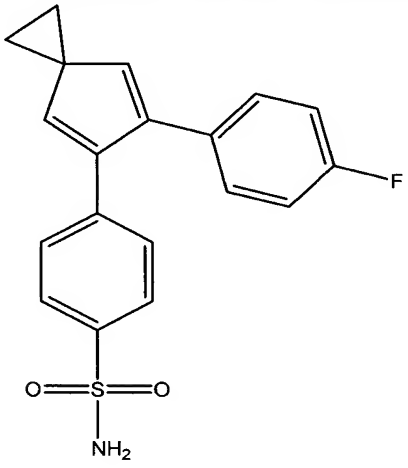
Compound Number	**Structural Formula**
B-106	 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-107	 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-108	 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl] spiro[2.4]hept-5-ene;

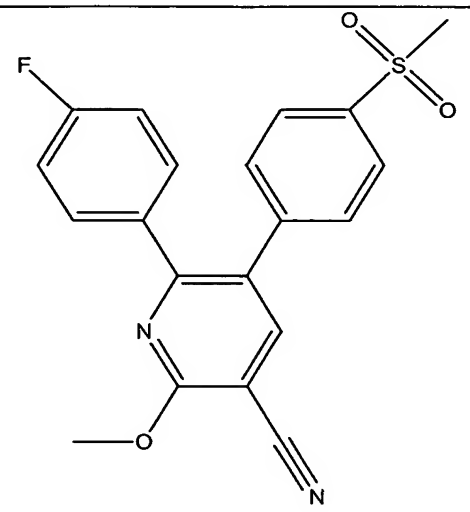
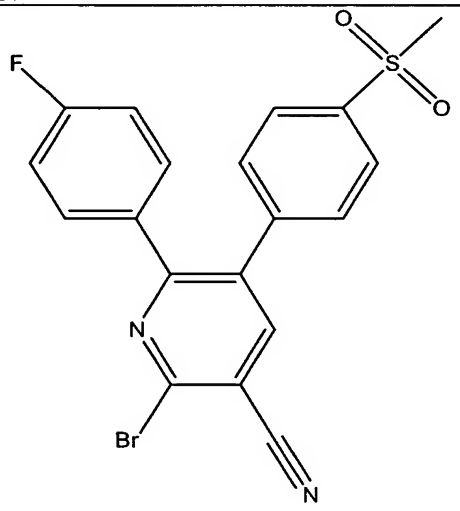
Compound Number	**Structural Formula**
B-109	 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-110	 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-111	 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

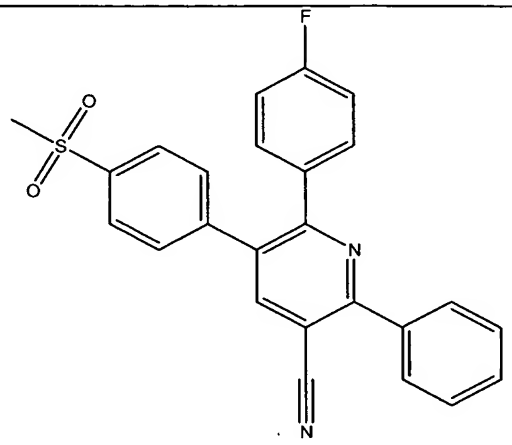
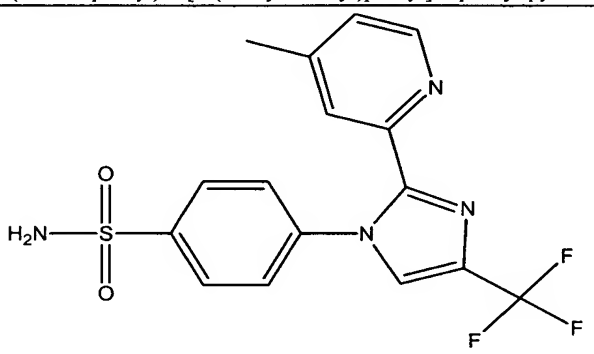
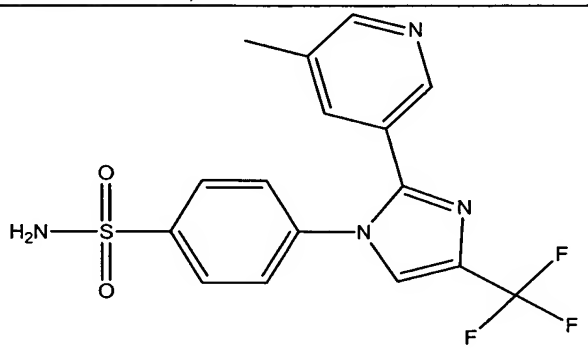
Compound Number	**Structural Formula**
B-112	 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
B-113	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
B-114	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

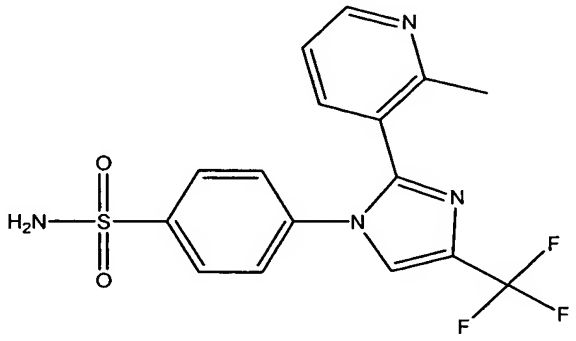
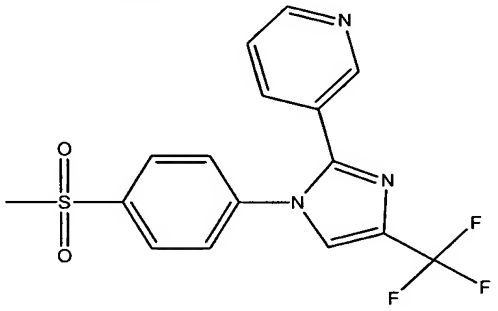
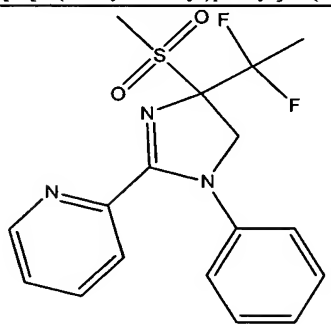
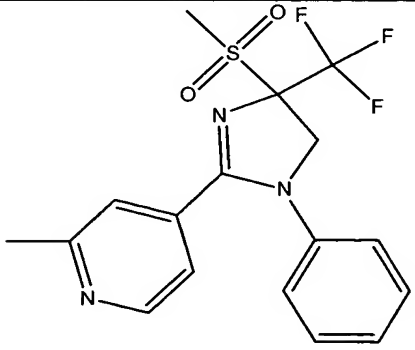
Compound Number	Structural Formula
B-115	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
B-116	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
B-117	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

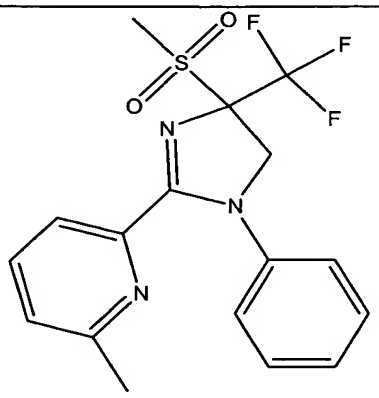
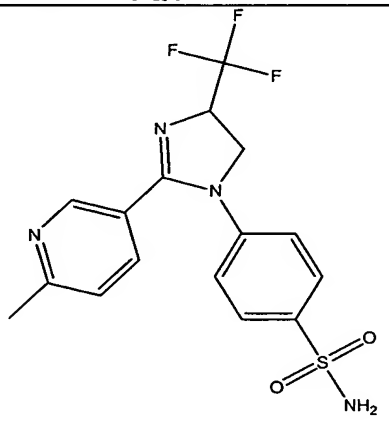
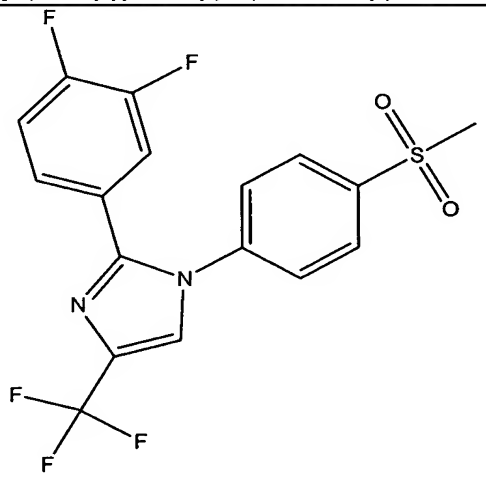
Compound Number	Structural Formula
B-118	 2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;
B-119	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
B-120	 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl) cyclopenta-2,4-dien-3-yl]benzene;

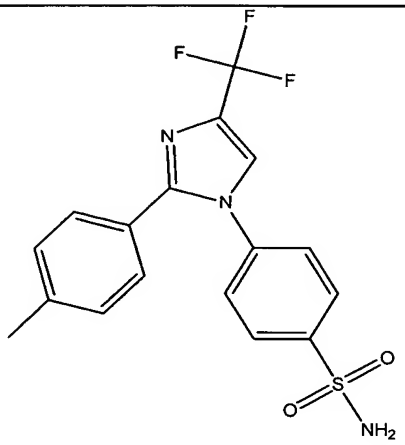
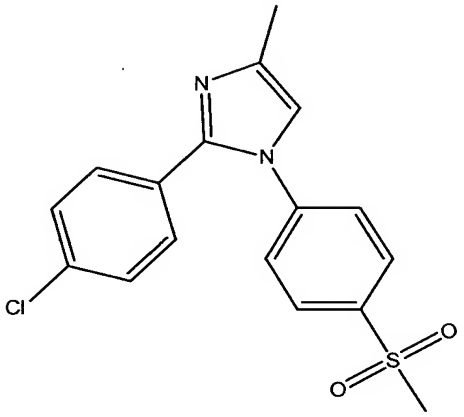
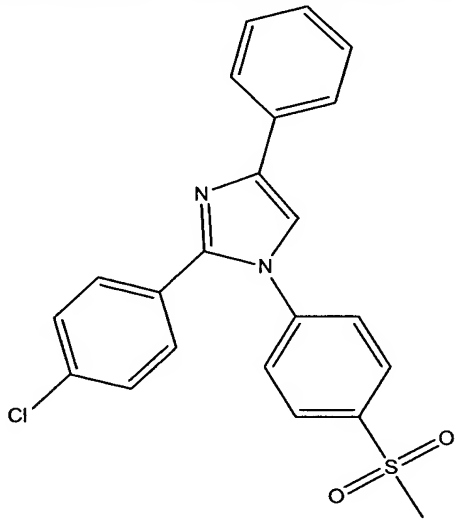
Compound Number	**Structural Formula**
B-121	 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl] benzenesulfonamide;
B-122	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
B-123	 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

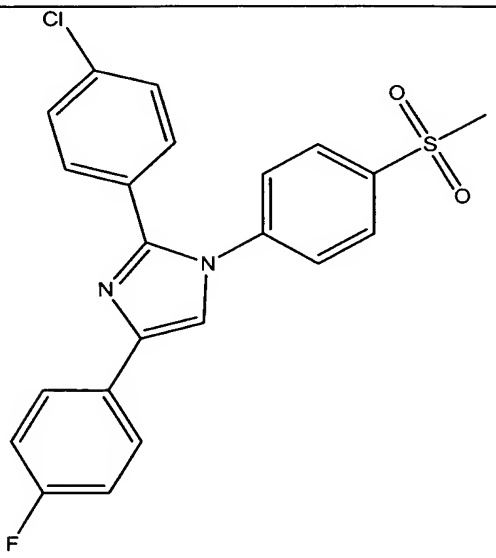
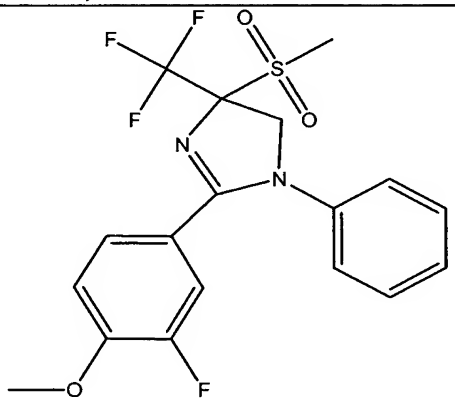
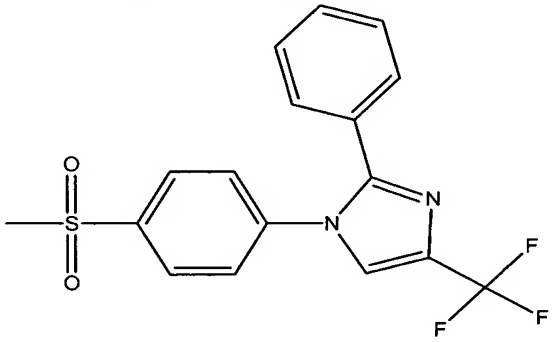
Compound Number	**Structural Formula**
B-124	 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile;
B-125	 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile;

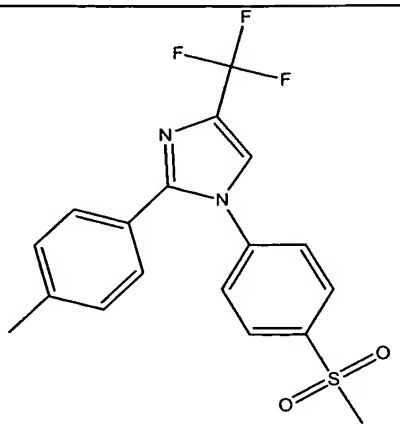
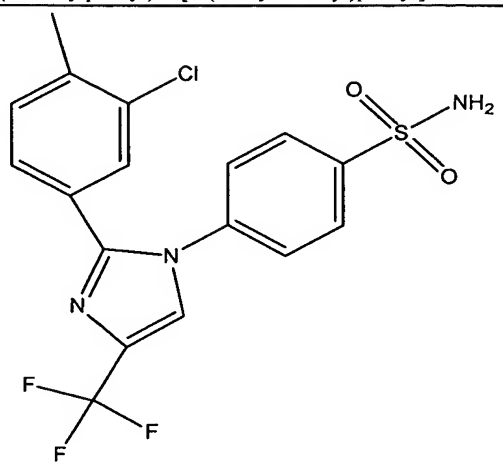
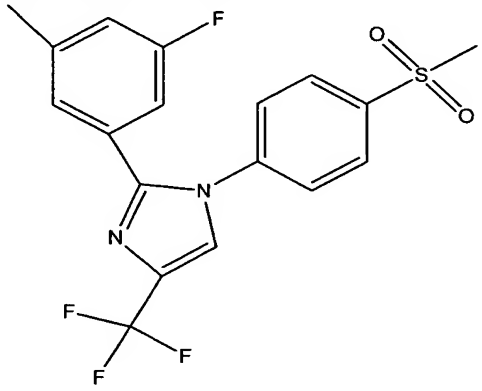
Compound Number	Structural Formula
B-126	 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;
B-127	 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;
B-128	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;

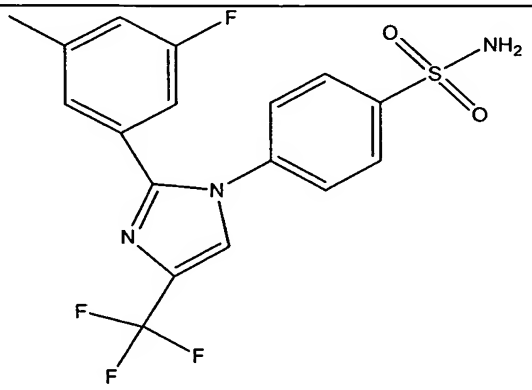
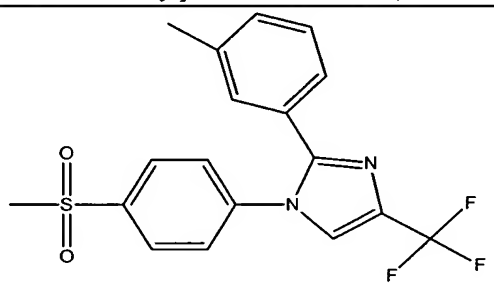
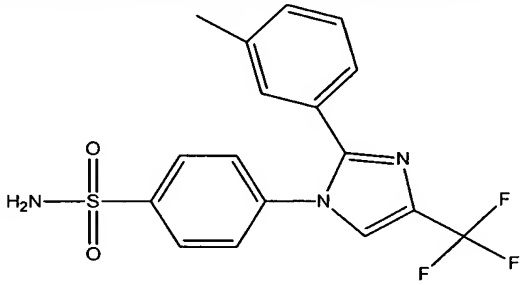
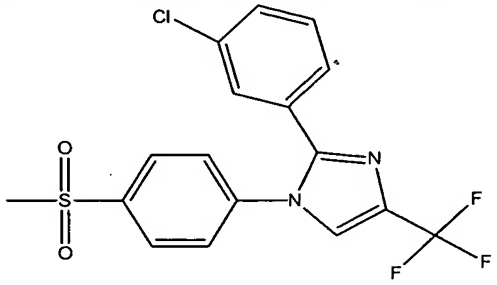
Compound Number	Structural Formula
B-129	 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;
B-130	 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
B-131	 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)]-1H-imidazol-2-yl]pyridine;
B-132	 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine;

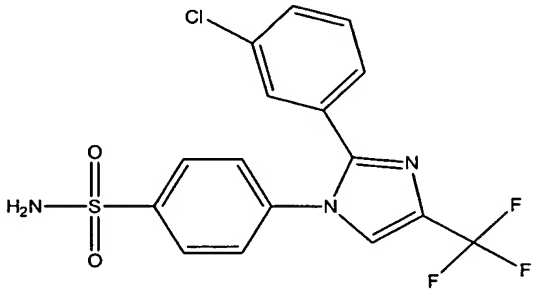
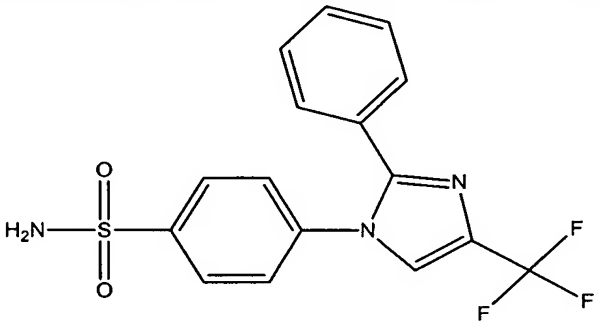
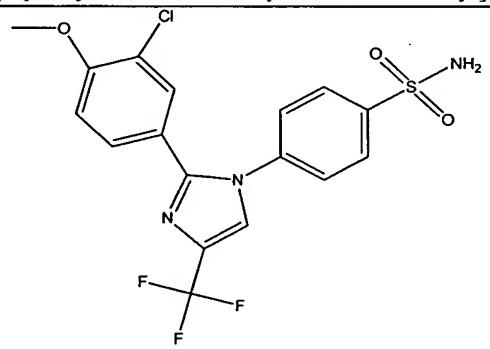
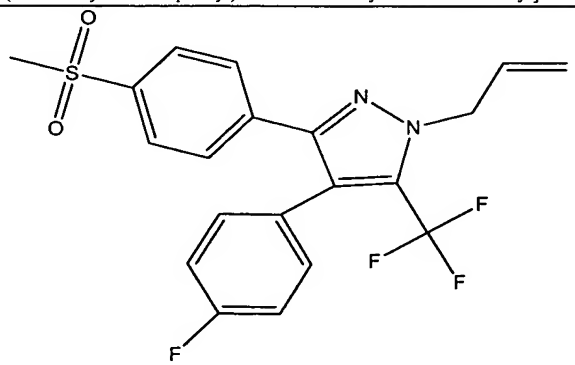
Compound Number	Structural Formula
B-133	 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine;
B-134	 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-135	 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole;

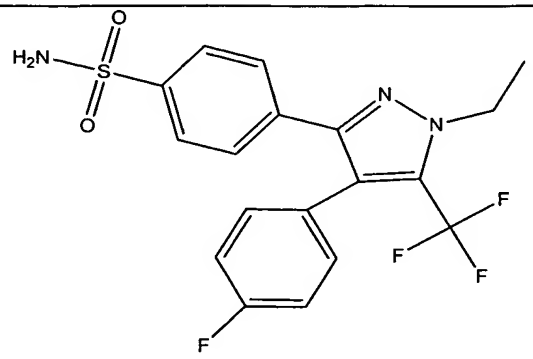
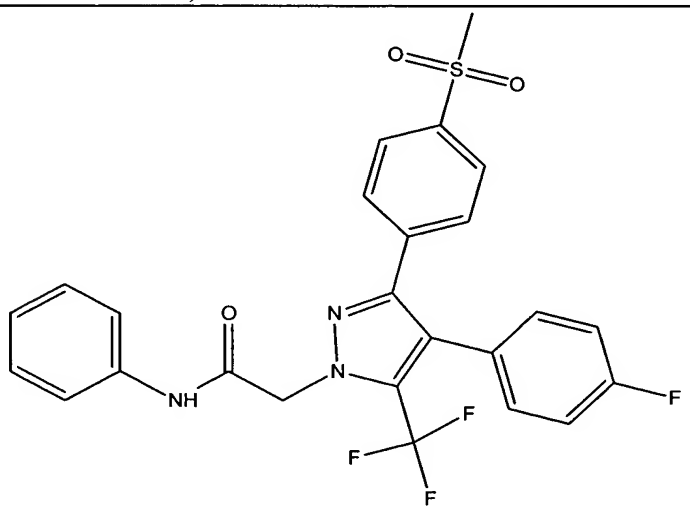
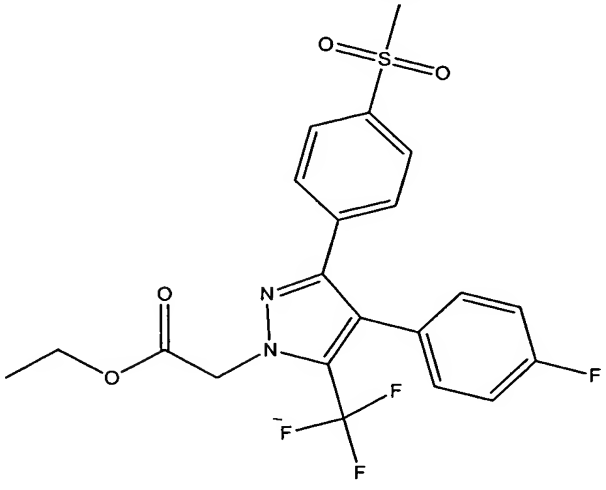
Compound Number	Structural Formula
B-136	 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-137	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
B-138	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

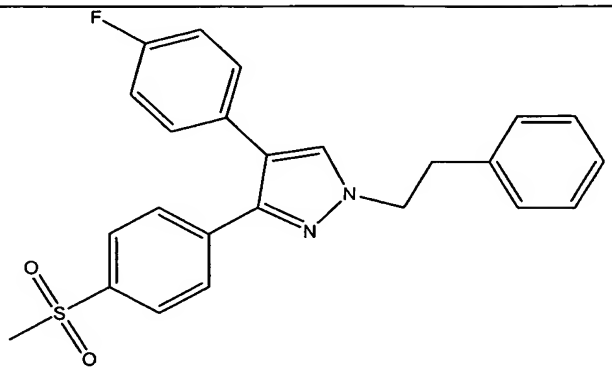
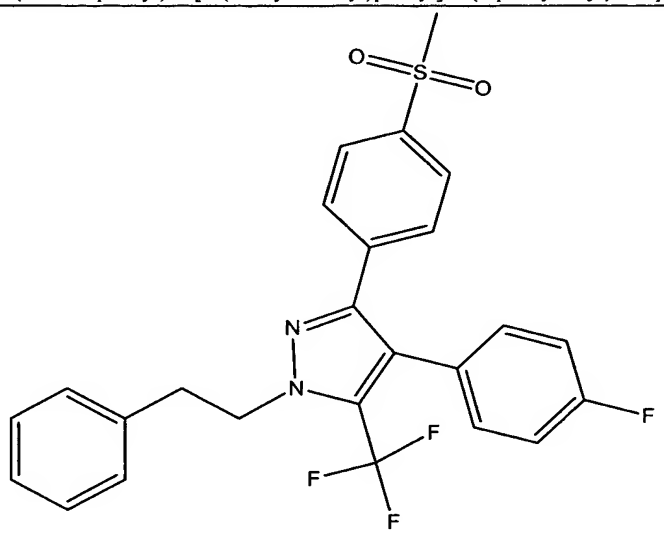
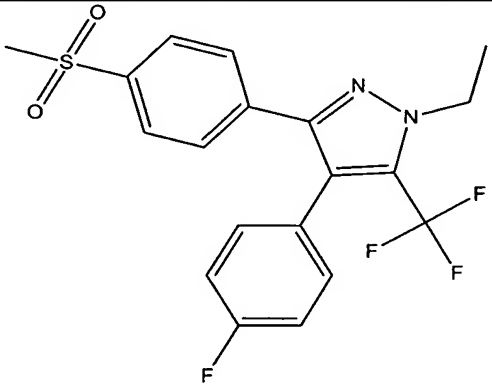
Compound Number	Structural Formula
B-139	 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl] -1H-imidazole;
B-140	 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl -4-(trifluoromethyl)]-1H-imidazole;
B-141	 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

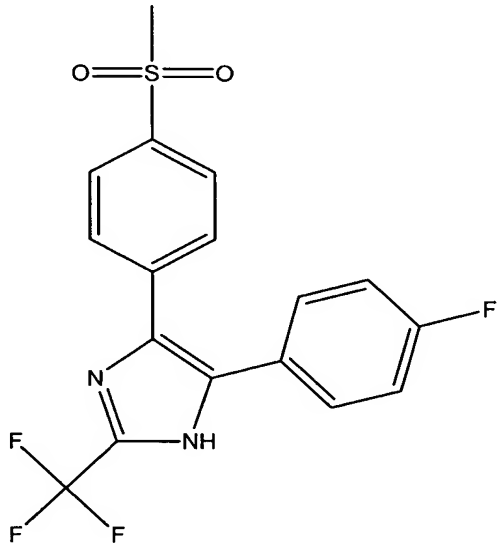
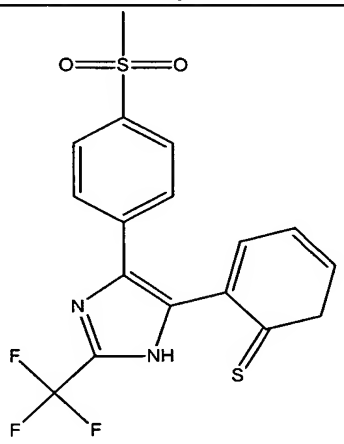
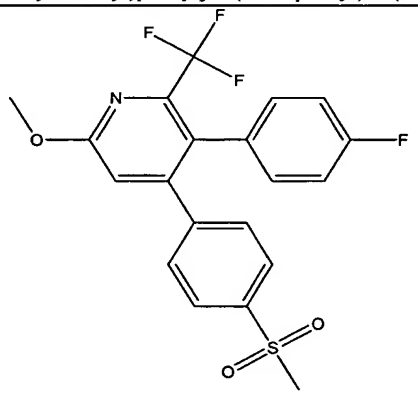
Compound Number	Structural Formula
B-142	 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
B-143	 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide;
B-144	 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole;

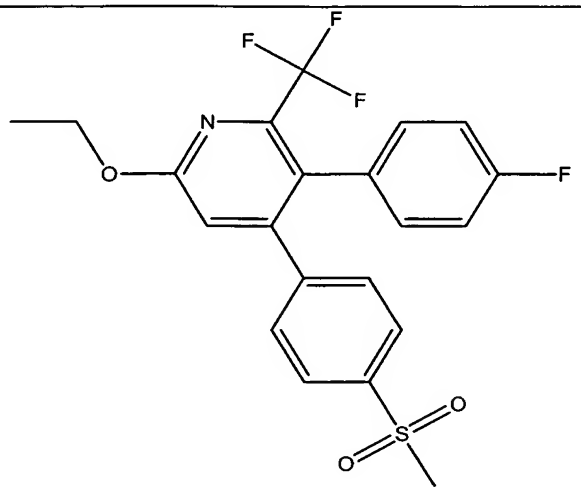
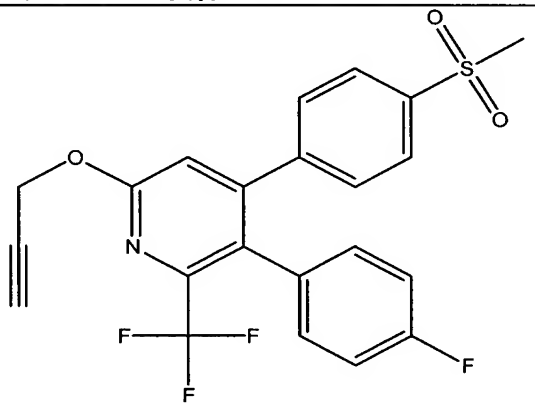
Compound Number	Structural Formula
B-145	 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl -1H-imidazole-1-yl]benzenesulfonamide;
B-146	 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
B-147	 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-148	 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole

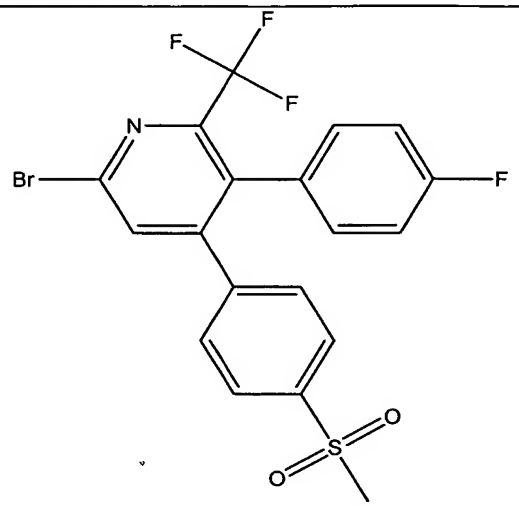
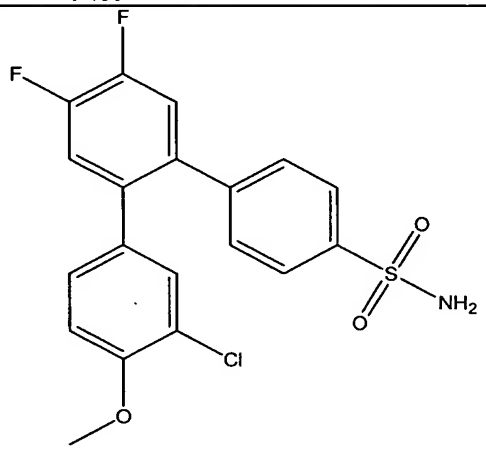
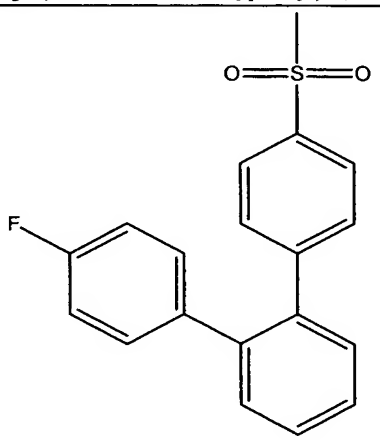
Compound Number	Structural Formula
B-149	 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-150	 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-151	 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-152	 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole;

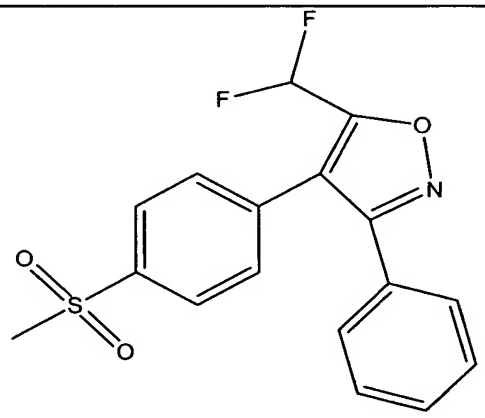
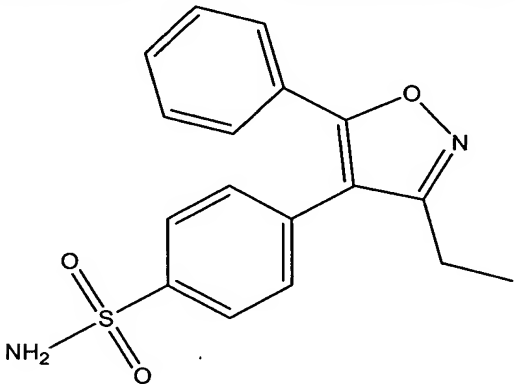
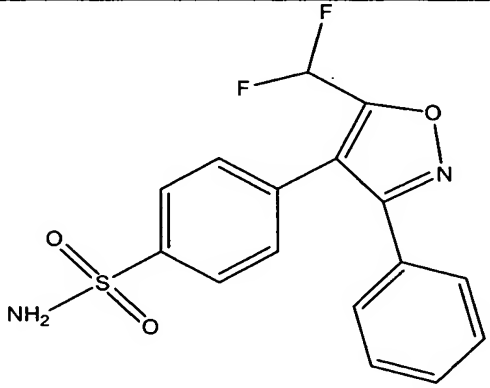
Compound Number	Structural Formula
B-153	 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl] benzenesulfonamide;
B-154	 N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
B-155	 ethyl[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

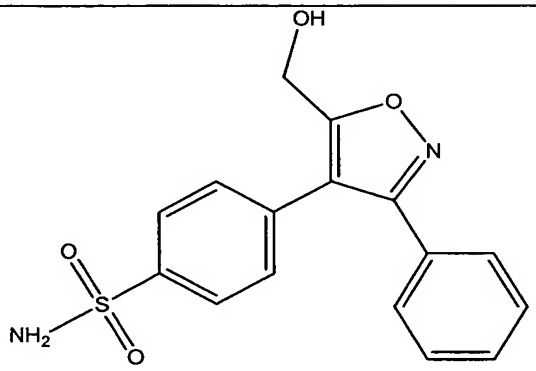
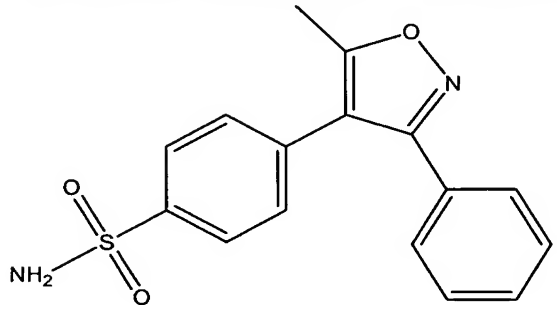
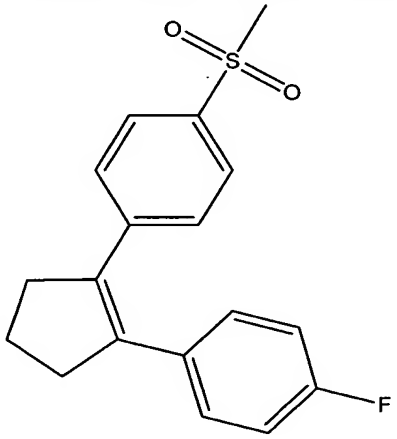
Compound Number	Structural Formula
B-156	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
B-157	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
B-158	 1-ethyl-4-(4-fluorophenyl)-3-[4-methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole;

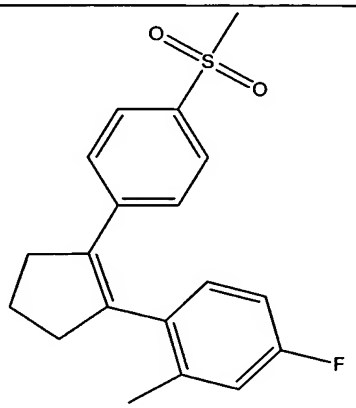
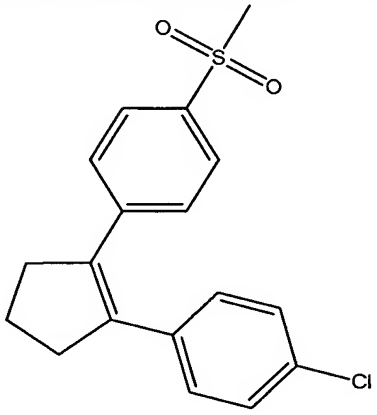
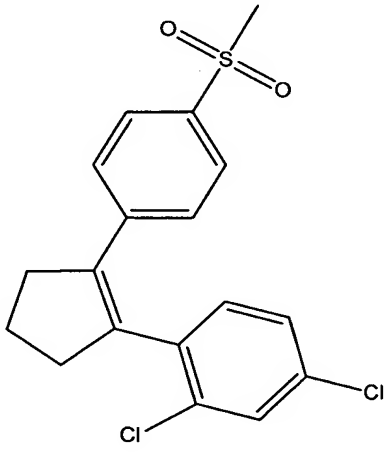
Compound Number	Structural Formula
B-159	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl) -2-trifluoromethyl-1H-imidazole;
B-160	 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
B-161	 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

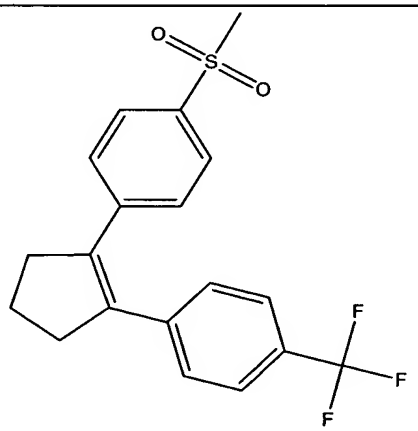
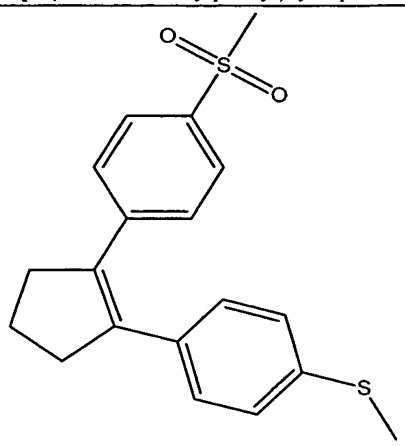
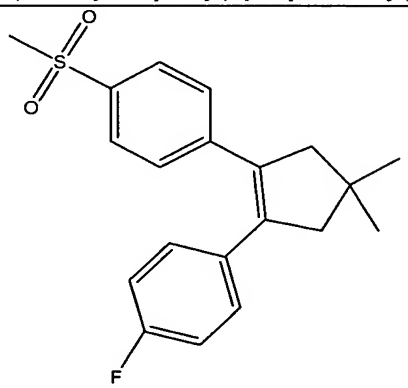
Compound Number	**Structural Formula**
B-162	 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine;
B-163	 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

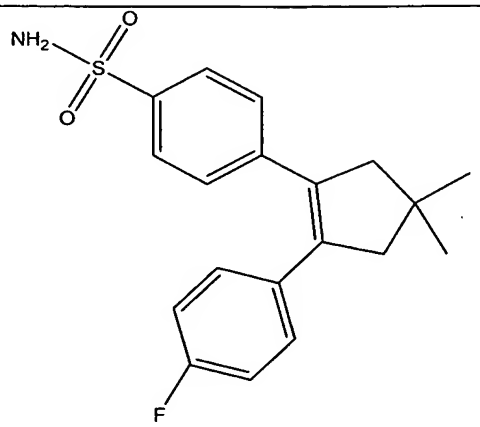
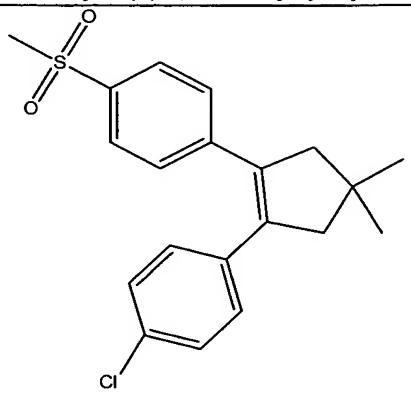
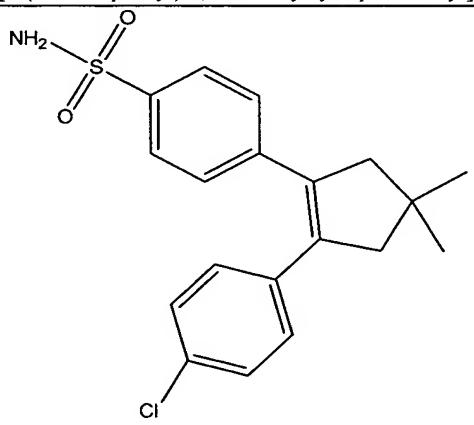
Compound Number	Structural Formula
B-164	 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine;
B-165	 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
B-166	 1-(4-fluorophenyl)-2-[4-methylsulfonyl)phenyl]benzene;

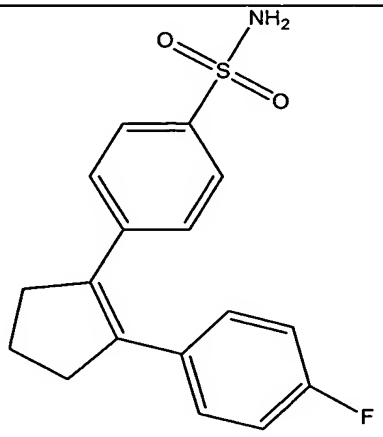
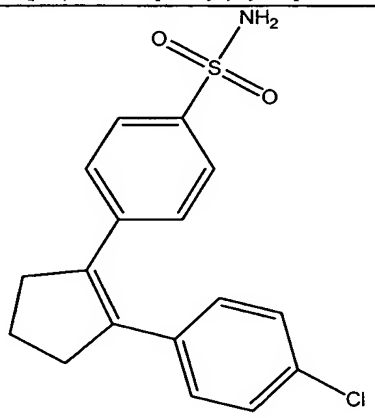
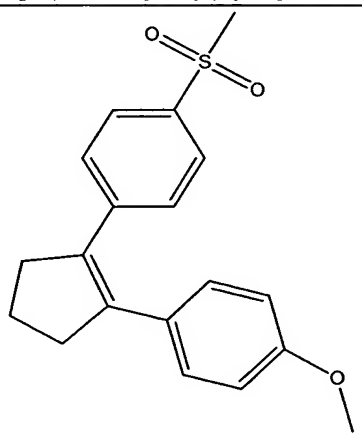
Compound Number	Structural Formula
B-167	 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;
B-168	 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
B-169	 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

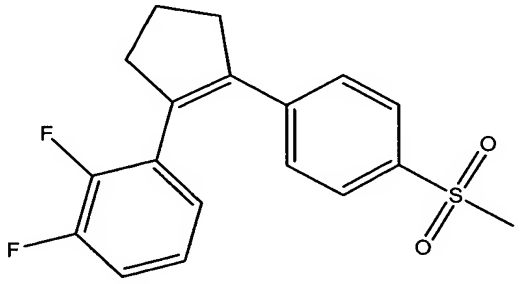
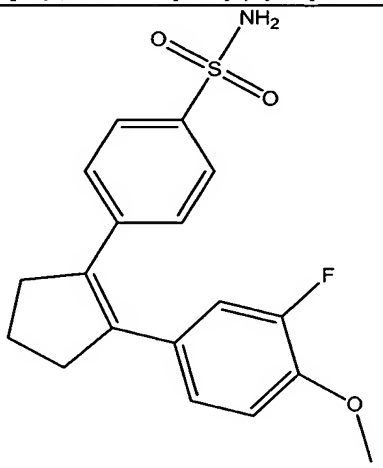
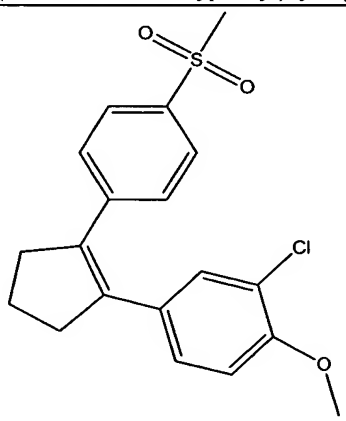
Compound Number	Structural Formula
B-170	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-171	 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
B-172	 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

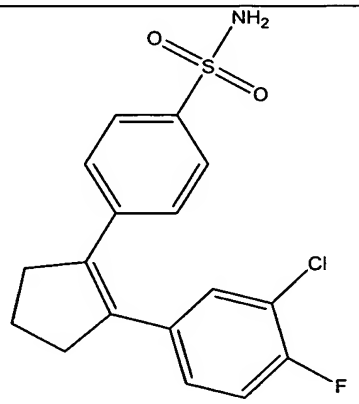
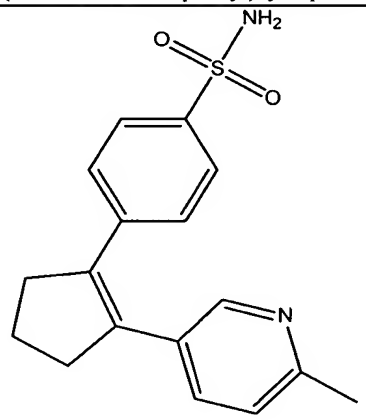
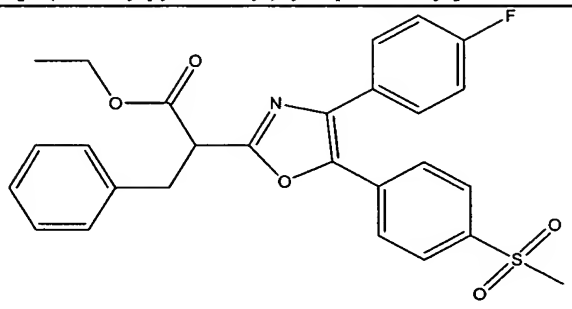
Compound Number	**Structural Formula**
B-173	 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-174	 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-175	 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

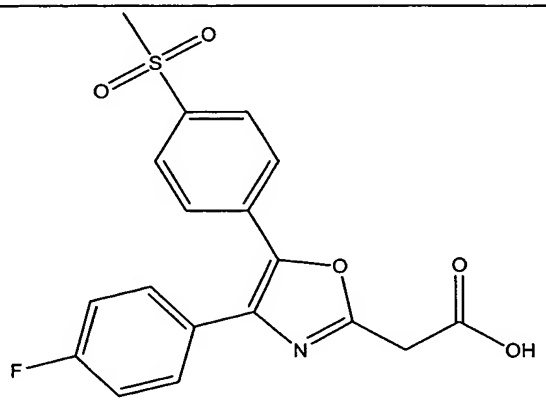
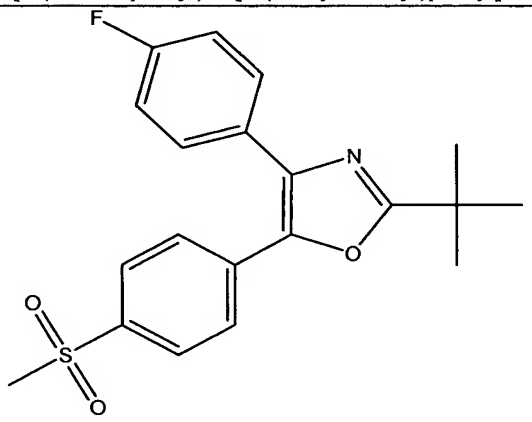
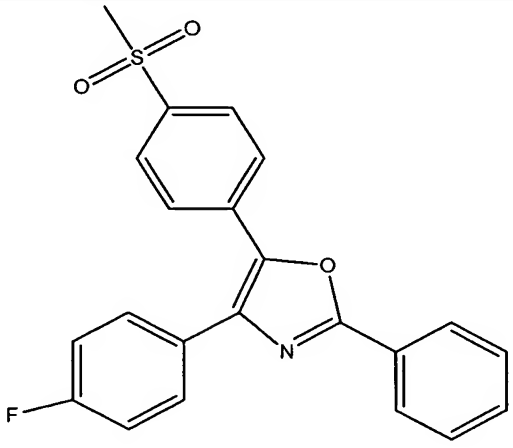
Compound Number	Structural Formula
B-176	 1-[2-(4-trifloromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-177	 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-178	 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

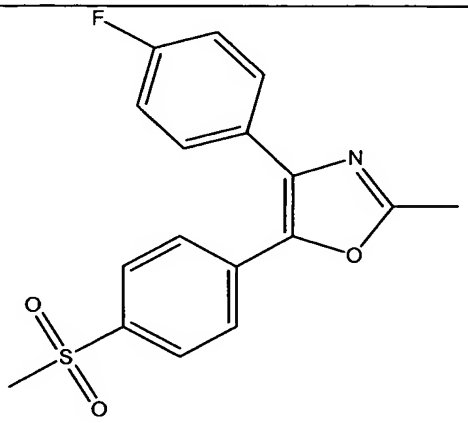
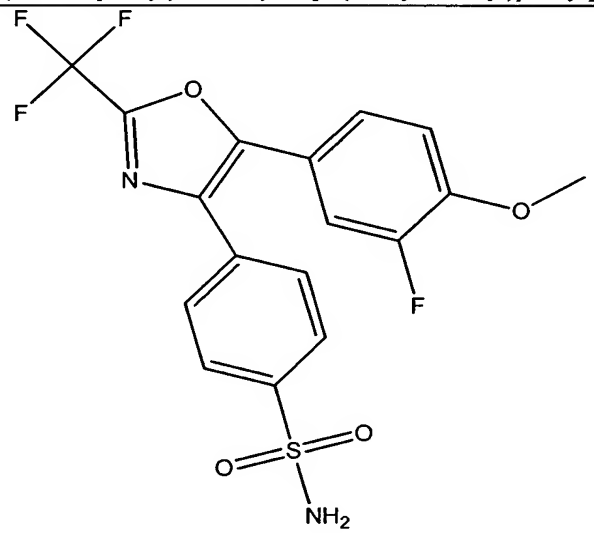
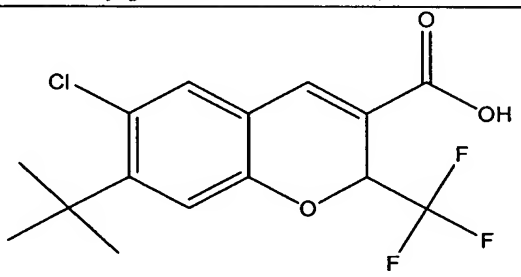
Compound Number	**Structural Formula**
B-179	 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
B-180	 1-[2-(3-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-181	 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

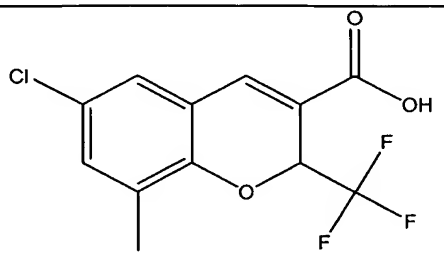
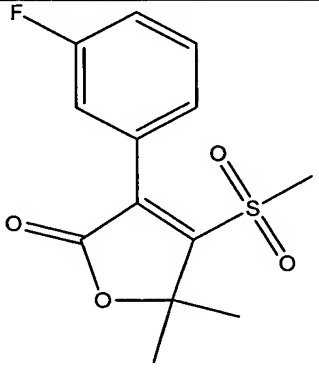
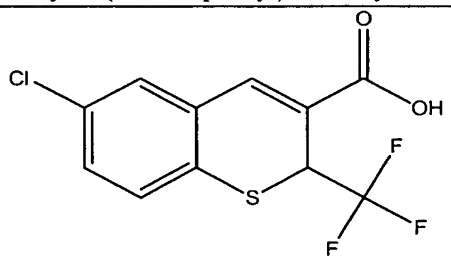
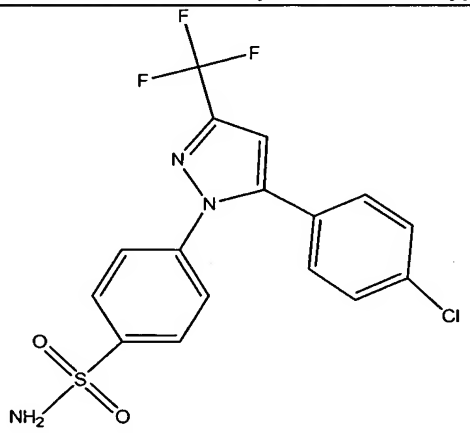
Compound Number	Structural Formula
B-182	 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-183	 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-184	 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

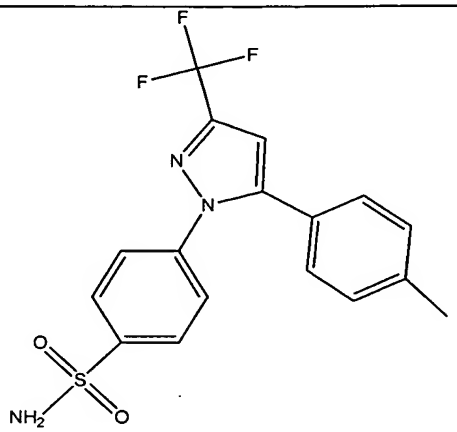
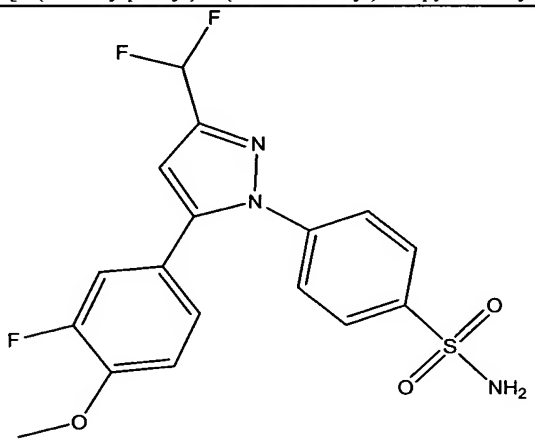
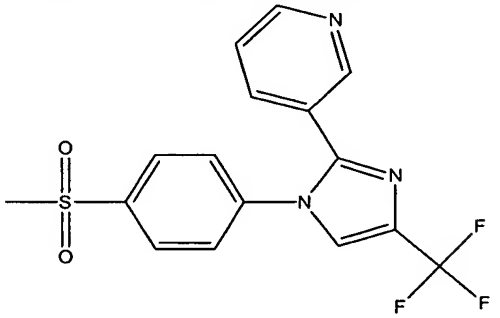
Compound Number	Structural Formula
B-185	 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-186	 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
B-187	 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

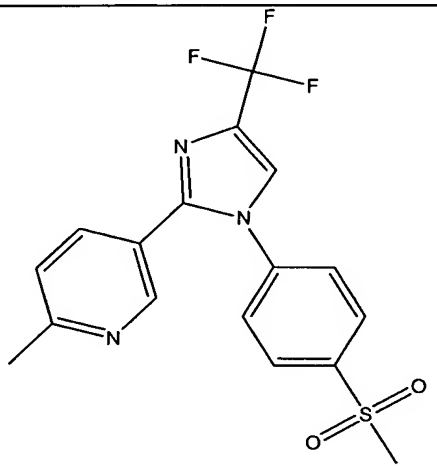
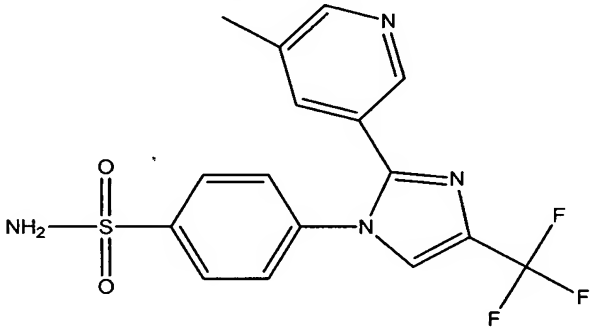
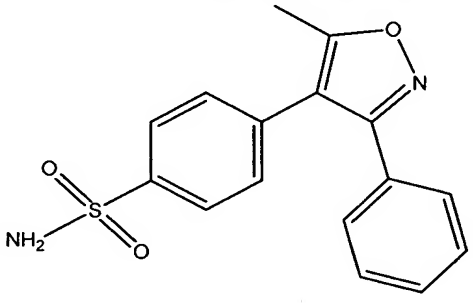
Compound Number	Structural Formula
B-188	 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-189	 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
B-190	 ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzyl-acetate;

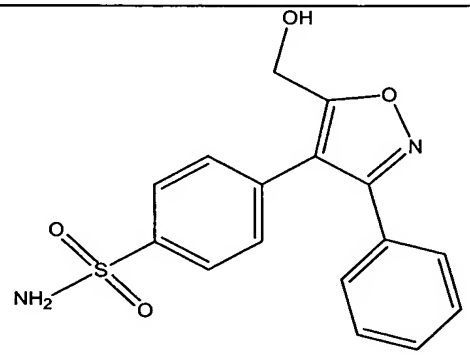
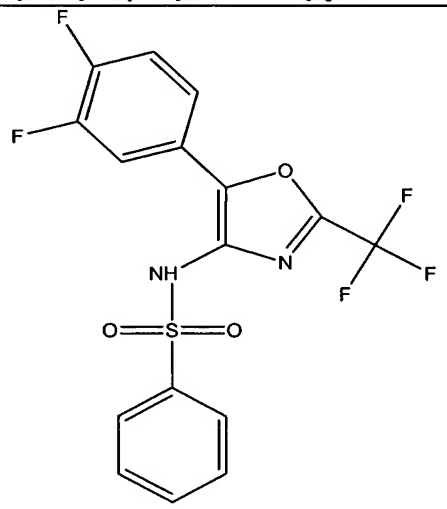
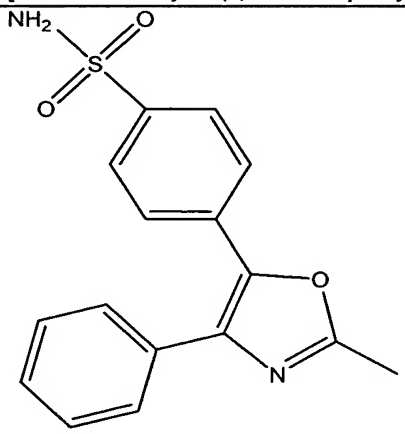
Compound Number	Structural Formula
B-191	 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;
B-192	 2-(tert-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
B-193	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

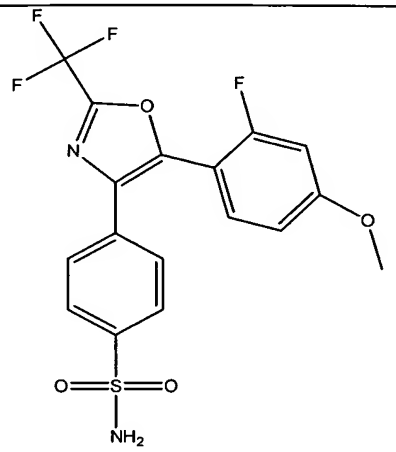
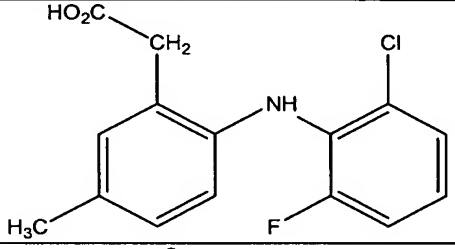
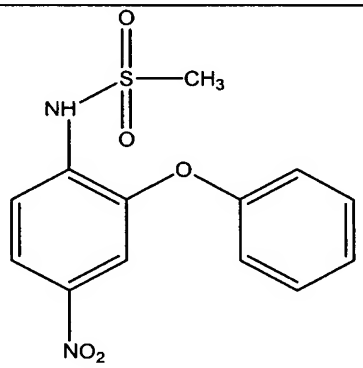
Compound Number	**Structural Formula**
B-194	 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;
B-195	 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl -4-oxazolyl]benzenesulfonamide;
B-196	 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H -1-benzopyran-3-carboxylic acid;

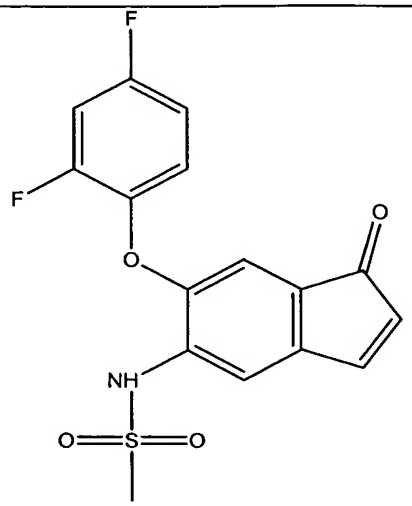
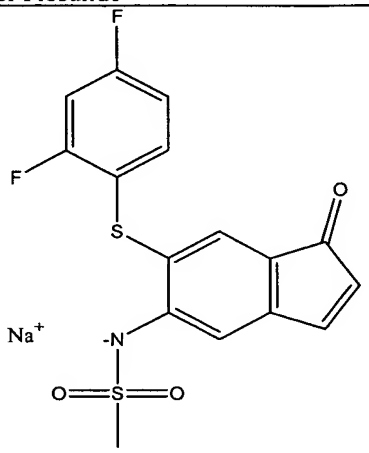
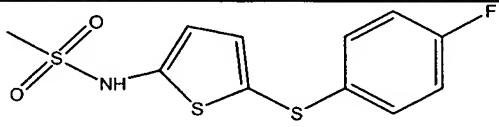
Compound Number	Structural Formula
B-197	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-198	 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone;
B-199	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
B-200	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

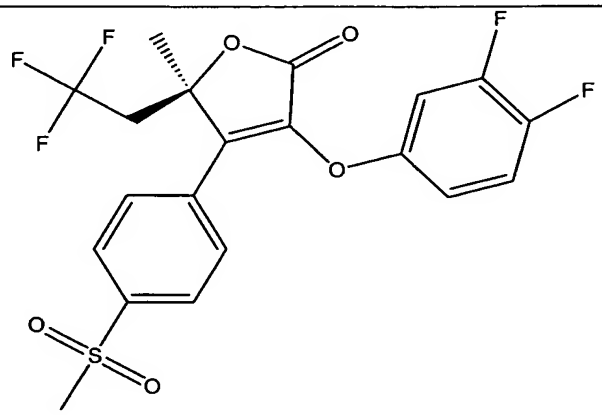
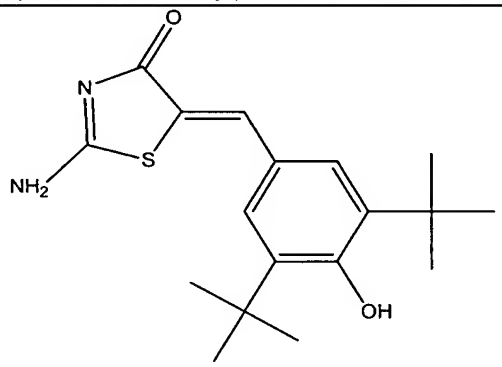
Compound Number	Structural Formula
B-201	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-202	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide;
B-203	 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

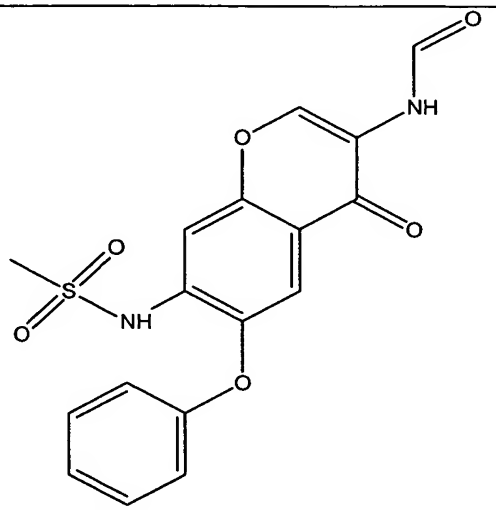
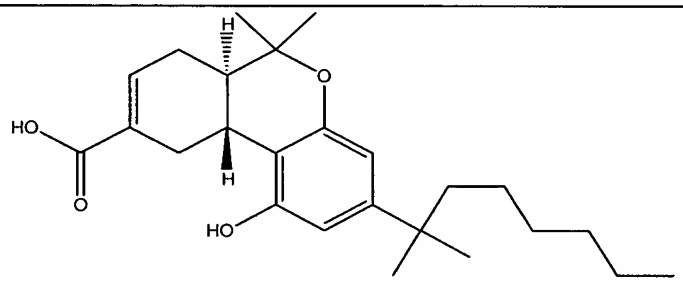
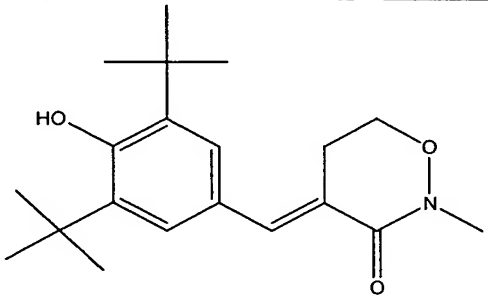
Compound Number	Structural Formula
B-204	 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl -1H-imidazol-2-yl]pyridine;
B-205	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide;
B-206	 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

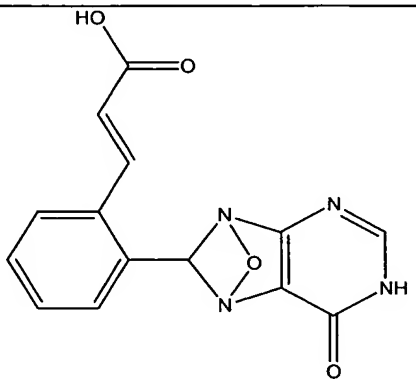
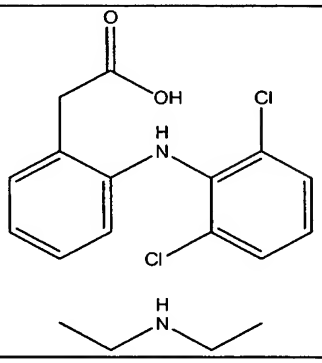
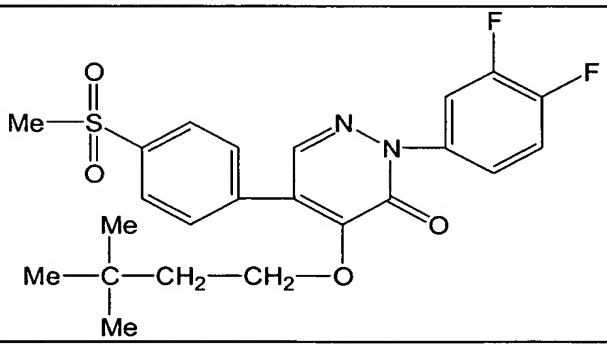
Compound Number	Structural Formula
B-207	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-208	 [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
B-209	 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide;

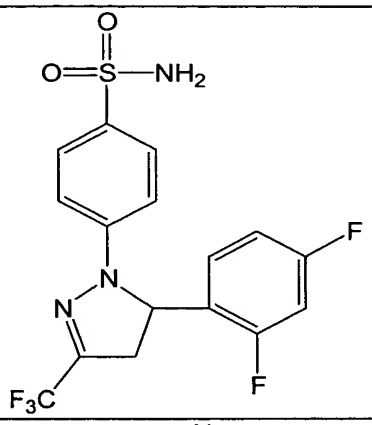
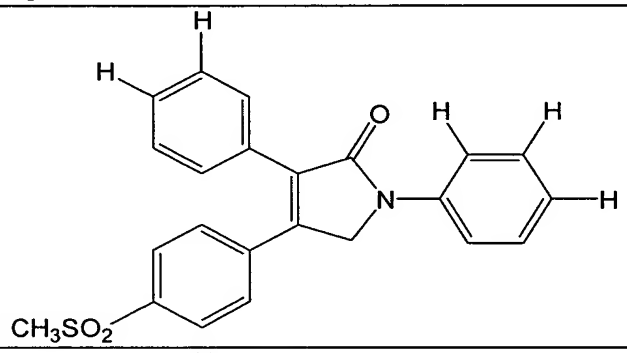
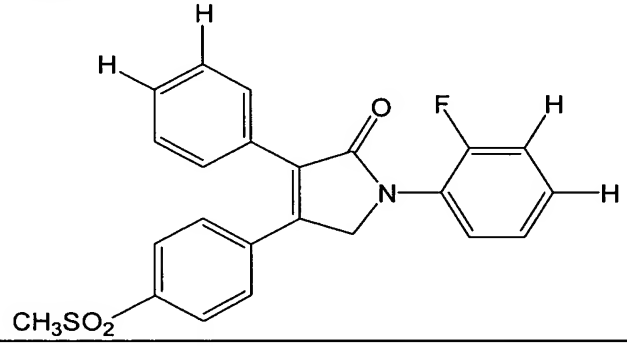
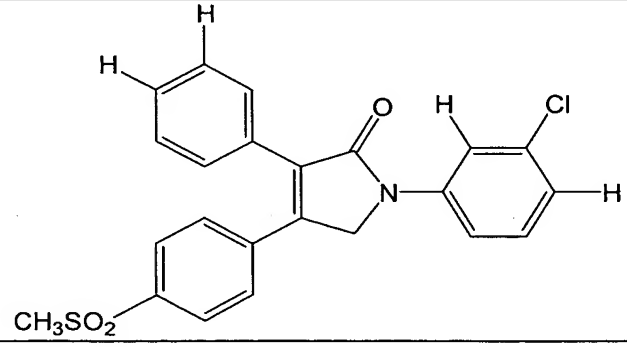
Compound Number	**Structural Formula**
B-210	 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
B-211	
B-212	 *N*-(4-nitro-2-phenoxy-phenyl)-methanesulfonamide or Nimesulide

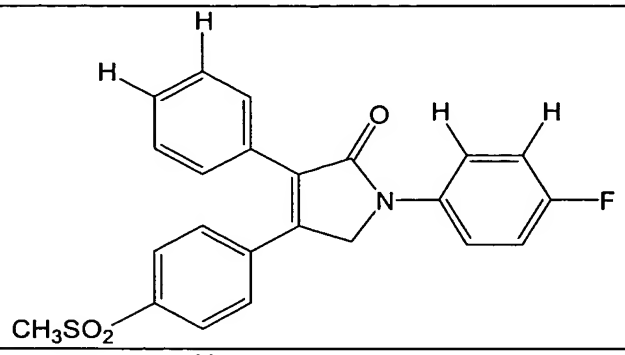
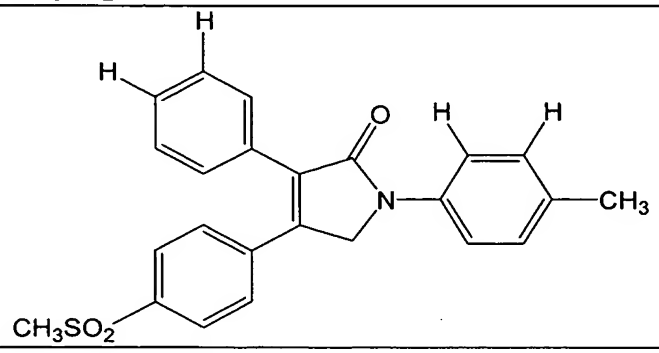
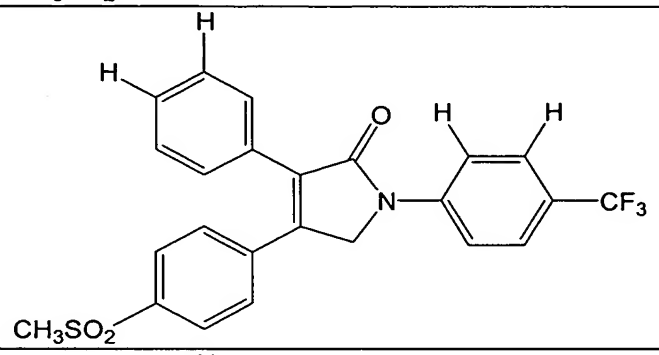
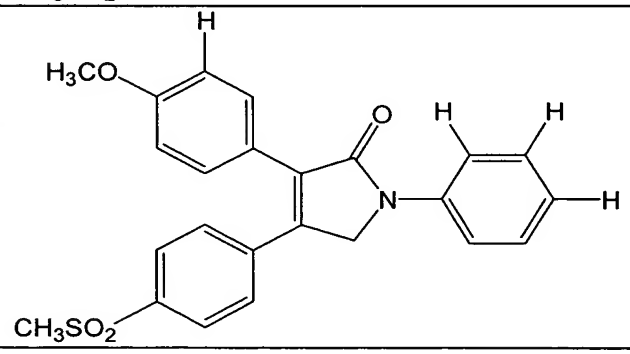
Compound Number	Structural Formula
B-213	 N-[6-(2,4-difluoro-phenoxy)-1-oxo-inden-5-yl]-methanesulfonamide or Flosulide
B-214	 *N*-[6-(2,4-difluoro-phenylsulfanyl)-1-oxo-1*H*-inden-5-yl]-methanesulfonamide, soldium salt, or L-745337
B-215	 N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide or RWJ-63556

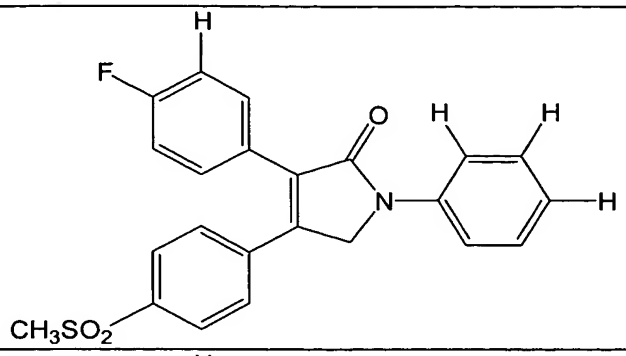
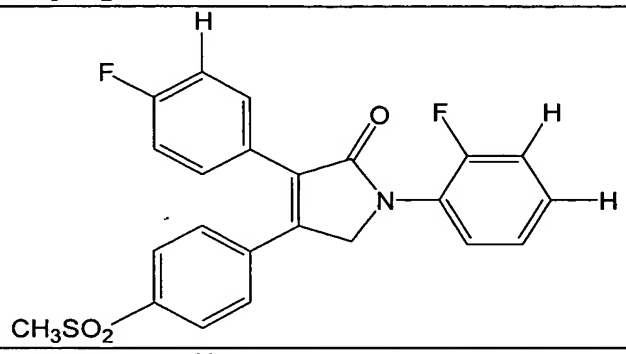
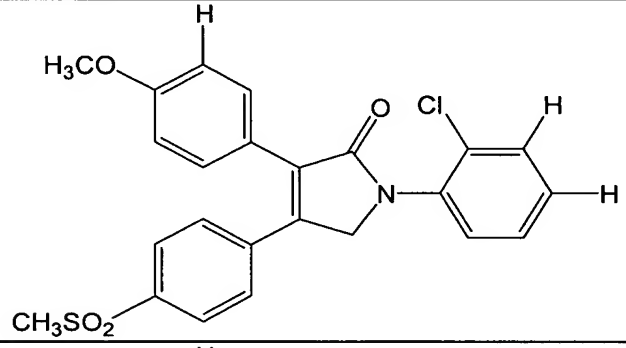
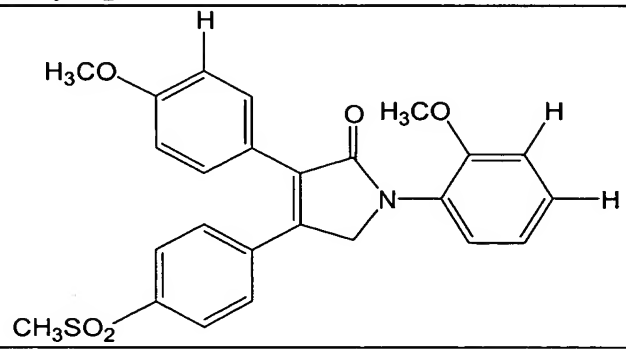
Compound Number	**Structural Formula**
B-216	 3-(3,4-difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl -5-(2,2,2-trifluoro-ethyl)-5*H*-furan-2-one or L-784512
B-217	 (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] -4(5H)-thiazolone or Darbufelone
B-218	CS-502
B-219	LAS-34475
B-220	LAS-34555
B-221	S-33516
B-222	SD-8381
B-223	L-783003

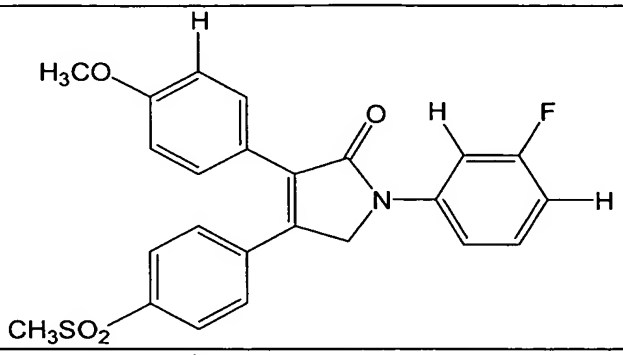
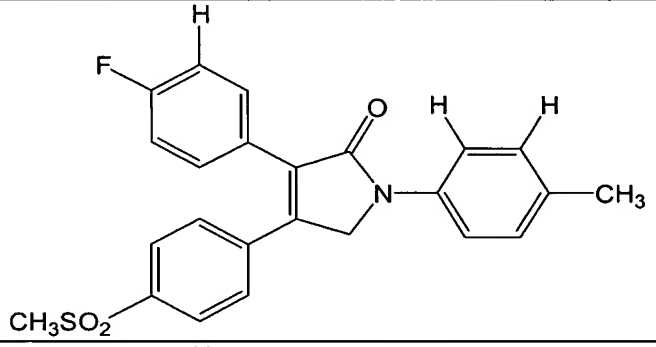
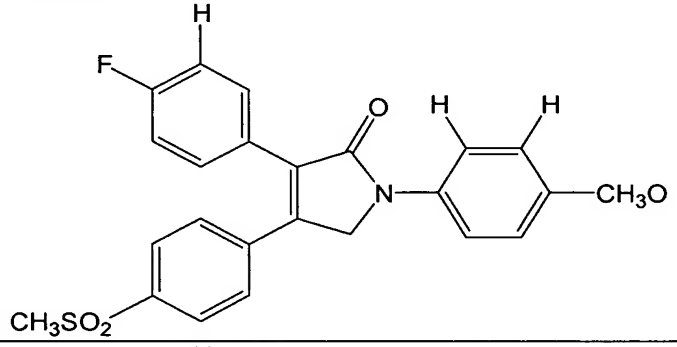
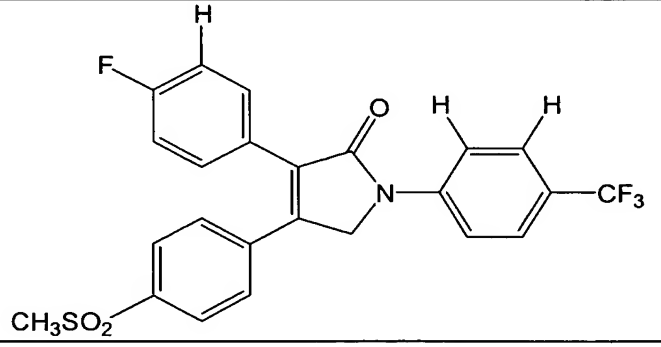
Compound Number	Structural Formula
B-224	 N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] -methanesulfonamide or T614
B-225	D-1367
B-226	L-748731
B-227	 (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethy l-6H-dibenzo[b,d]pyran-9-carboxylic acid or CT3
B-228	CGP-28238
B-229	 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389

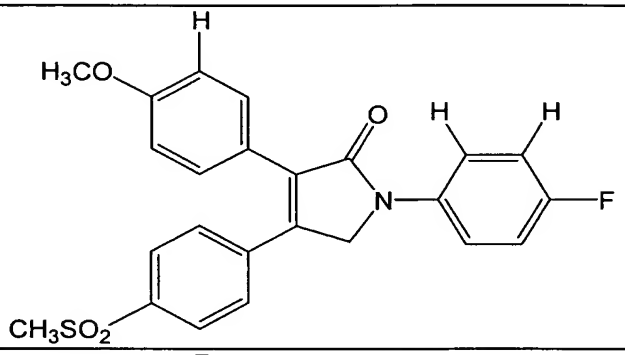
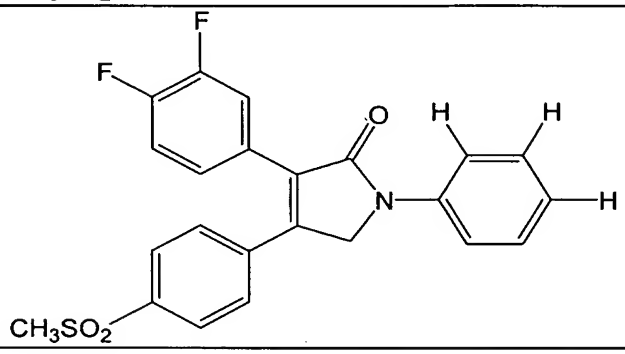
Compound Number	**Structural Formula**
B-230	GR-253035
B-231	 2-(6-dioxo-9H-purin-8-yl)cinnamic acid
B-232	S-2474
B-233	
B-234	

Compound Number	**Structural Formula**
B-235	
B-236	
B-237	
B-238	

Compound Number	Structural Formula
B-239	
B-240	
B-241	
B-242	

Compound Number	Structural Formula
B-243	
B-244	
B-245	
B-246	

Compound Number	Structural Formula
B-247	
B-248	
B-249	
B-250	

Compound Number	Structural Formula
B-251	
B-252	

[0376] The cyclooxygenase-2 selective inhibitor employed in the present invention can exist in tautomeric, geometric or stereoisomeric forms. Generally speaking, suitable cyclooxygenase-2 selective inhibitors that are in tautomeric, geometric or stereoisomeric forms are those compounds that inhibit cyclooxygenase-2 activity by about 25%, more typically by about 50%, and even more typically, by about 75% or more when present at a concentration of 100 μM or less. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof. Pharmaceutically acceptable salts of such tautomeric, geometric or stereoisomeric forms are also included within the invention. The terms "cis" and "trans", as used herein, denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans"). Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms. Furthermore, some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures or R and S forms for each stereocenter present.

[0377] The cyclooxygenase-2 selective inhibitors utilized in the present invention may be in the form of free bases or pharmaceutically acceptable acid addition salts thereof.

The term "pharmaceutically-acceptable salts" are salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt may vary, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds for use in the present methods may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of use in the present methods include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound of any Formula set forth herein.

[0378] The cyclooxygenase-2 selective inhibitors of the present invention can be formulated into pharmaceutical compositions and administered by a number of different means that will deliver a therapeutically effective dose. Such compositions can be administered orally, parenterally, by inhalation spray, rectally, intradermally, transdermally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania (1975), and Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y. (1980).

[0379] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, can be formulated according to the known art using suitable

dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, and polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

[0380] Suppositories for rectal administration of the compounds discussed herein can be prepared by mixing the active agent with a suitable non-irritating excipient such as cocoa butter, synthetic mono-, di-, or triglycerides, fatty acids, or polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature, and which will therefore melt in the rectum and release the drug.

[0381] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

[0382] For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium

chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

[0383] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[0384] The amount of active ingredient that can be combined with the carrier materials to produce a single dosage of the cyclooxygenase-2 selective inhibitor will vary depending upon the patient and the particular mode of administration. In general, the pharmaceutical compositions may contain a cyclooxygenase-2 selective inhibitor in the range of about 0.1 to 2000 mg, more typically, in the range of about 0.5 to 500 mg and still more typically, between about 1 and 200 mg. A daily dose of about 0.01 to 100 mg/kg body weight, or more typically, between about 0.1 and about 50 mg/kg body weight and even more typically, from about 1 to 20 mg/kg body weight, may be appropriate. The daily dose is generally administered in one to about four doses per day.

[0385] In one embodiment, when the cyclooxygenase-2 selective inhibitor comprises rofecoxib, it is typical that the amount used is within a range of from about 0.15 to about 1.0 mg/day·kg, and even more typically, from about 0.18 to about 0.4 mg/day·kg.

[0386] In still another embodiment, when the cyclooxygenase-2 selective inhibitor comprises etoricoxib, it is typical that the amount used is within a range of from about 0.5 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0387] Further, when the cyclooxygenase-2 selective inhibitor comprises celecoxib, it is typical that the amount used is within a range of from about 1 to about 20 mg/day·kg, even more typically, from about 1.4 to about 8.6 mg/day·kg, and yet more typically, from about 2 to about 3 mg/day·kg.

[0388] When the cyclooxygenase-2 selective inhibitor comprises valdecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0389] In a further embodiment, when the cyclooxygenase-2 selective inhibitor comprises parecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 1 to about 3 mg/day·kg.

[0390] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

[0391] In another embodiment, the pharmaceutical composition containing a suitable cyclooxygenase-2 selective inhibitor can also be administered locally at the site of vascular occlusion. For example and without limitation, a cyclooxygenase-2 selective inhibitor can be incorporated into a stent to be implanted into the vasculature. The stent can be coated with a degradable polymer into which the cyclooxygenase-2 selective inhibitor has been incorporated. As the polymer slowly degrades, it would release the cyclooxygenase-2 selective inhibitor into the area surrounding the stent. An example of a stent coated with a degradable polymer can be found in Strecker et al. (*Cardiovasc. Intervent. Radiol.*, 21:487-496, 1998). Alternatively, local administration can be achieved by the use of microspheres that are implanted into the vascular wall surrounding the occlusion. An example of the use of microspheres for administration of compounds to the vascular wall can be found in Valero et al. (*J. Cardiovasc. Pharmacol.* 31:513-519, 1998). Also included are catheter-based local delivery systems. Non-limiting examples of catheter-based local delivery systems include hydrophilic-coated catheter balloons that absorb the cyclooxygenase-2 selective inhibitor and then release it when pressed against the vessel wall, and fenestrated balloon catheters that use a high velocity jet to spray the cyclooxygenase-2 selective inhibitor against the vessel wall and thus embed it in the vessel wall

[0392] The timing of the administration of the cyclooxygenase-2 selective inhibitor can also vary. For example, the cyclooxygenase-2 selective inhibitor can be administered beginning at a time prior to the vaso-occlusive event, at the time of the vaso-occlusive event, or at a time after the vaso-occlusive event. Administration can be by a single dose, or more preferably the cyclooxygenase-2 selective inhibitor is given over an extended period. It is preferred that administration of the cyclooxygenase-2 selective inhibitor extend for a period after the vaso-occlusive event. In one embodiment, administration is continued for six months following the vaso-occlusive event. In other embodiments, administration of the cyclooxygenase-2 selective inhibitor is continued for 1 week, 2 weeks, 1 month, 3 months, 9 months, or one year after the vaso-occlusive event. In one embodiment, administration of a cyclooxygenase-2 selective inhibitor is continued throughout the life of the subject following the vaso-occlusive event.

CALCIUM MODULATING AGENT

[0393] In addition to a cyclooxygenase-2 selective inhibitor, the composition of the invention also includes a calcium modulating agent. A number of different calcium modulating agents may be employed in the present invention. In some embodiments, the calcium modulating agent will inhibit an increase in intracellular calcium ion levels following ischemic-mediated central nervous system damage or central nervous system damage resulting from traumatic injury. In other embodiments, the calcium modulating agent may bind to intracellular calcium ions and inhibit calcium from acting as an intracellular secondary messenger.

[0394] One aspect of the invention encompasses calcium modulating agents that inhibit the intracellular passage of Ca^{2+} ions through one or more calcium channels. The agent may be a calcium channel receptor antagonist or a derivative or analog of a calcium channel receptor antagonist.

[0395] In one embodiment, the calcium modulating agent inhibits the intracellular passage of Ca^{2+} ions through a voltage gated calcium channel. Voltage gated calcium channels are a diverse group of multi-subunit proteins that are composed of a pore forming subunit (α_1) with $\alpha_2\delta$, β, and γ auxiliary subunits. A number of isoforms have been identified for each subunit and in particular, for the α_1 subunit. In a voltage gated channel, the "opening" to allow an influx of Ca^{2+} ions into the cell requires a depolarization to a certain level of the potential difference between the inside of the cell bearing the channel and the extracellular medium bathing the cell. The voltage gated calcium channel may be high-voltage activated (HVA), low-voltage activated (LVA) or a any combination thereof. Generally speaking, in a human subject, calcium channels that are considered LVA typically open in response to a depolarization of less than about 25 mV. Calcium channels that are considered HVA, on-the-other-hand, typically open in response to a depolarization of greater than about 25 mV and more typically, greater than about 50 mV. HVA and LVA channels are further classified as L-type, N-type, P/Q-type, R-type or T-type based upon each channel's particular biophysical and pharmacological properties. Representative properties for each type of channel are shown in Table Z.

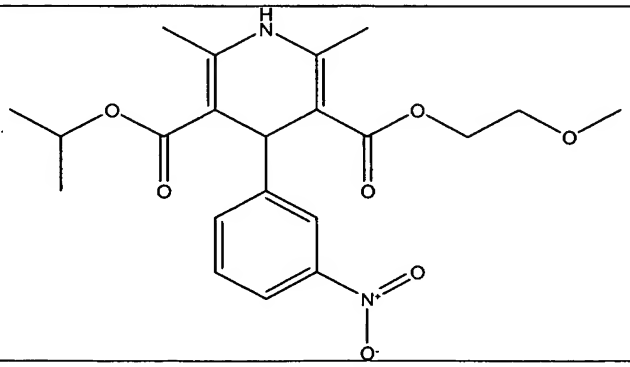
TABLE Z

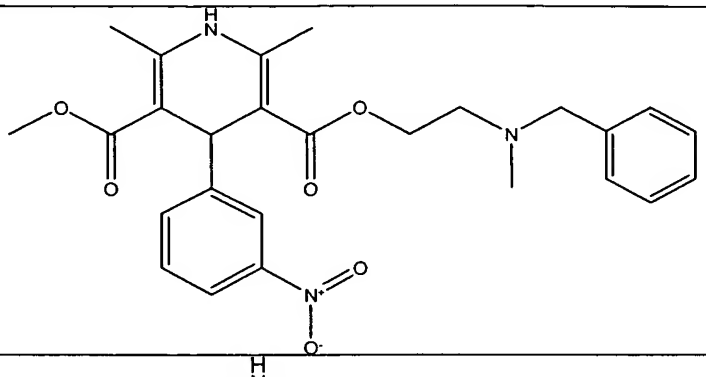
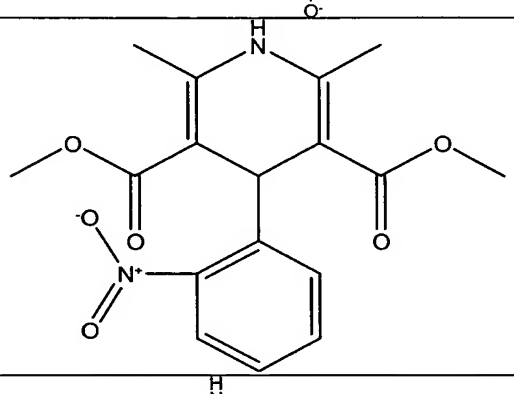
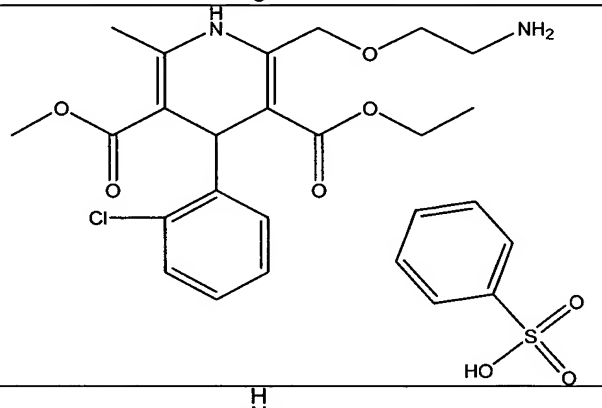
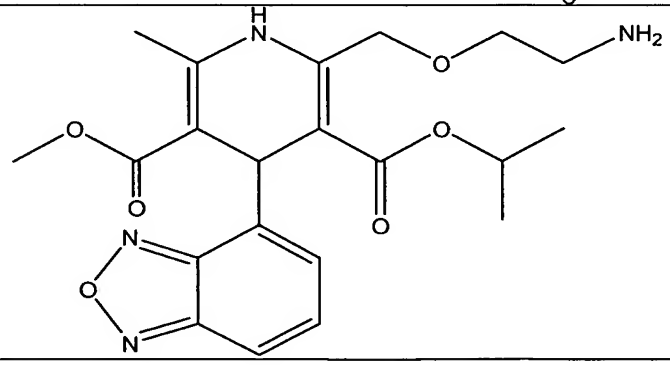
PROPERTIES OF THE DIFFERENT CHANNEL TYPES

Name	Type	α_1 subunit	Gene Symbol	Voltage-Dependent Inactivation During Step	Steady-State Inactivation V50 (mV)	Single Channel Conductance (pS)
L	HVA	α_{1S} α_{1C} α_{1D} α_{1F}	CACNA1S CACNA1C CACNA1D CACNA1F	None (Ca^{2+} dependent)	-20	24
N	HVA	α_{1B}	CACNA1B	Intermediate	-50	13-20
P	HVA	α_{1A}	CACNA1A	None	-5	10-18
Q	HVA	α_{1A}	CACNA1A	Intermediate	-45	NA
R	H/LVA	α_{1E}	CACNA1E	Fast (τ=20-30ms)	-15	NA
T	LVA	α_{1G} α_{1L} α_{1H}	CACNA1G CACNA1H	Fast (τ=20-40ms)	-70	8

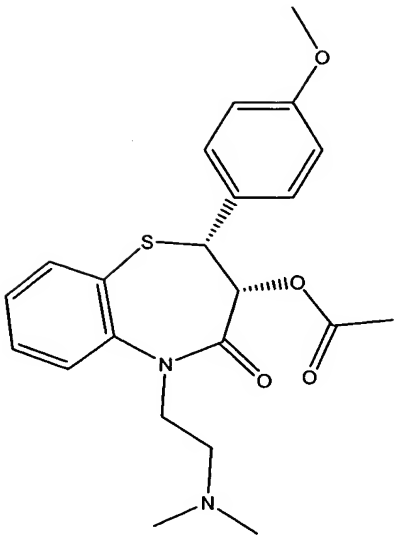
[0396] One embodiment, as detailed above, encompasses agents that inhibit calcium ion passage through a HVA channel. In one alternative of this embodiment, the agent inhibits the passage of calcium ions through a L-type channel. Typically, these agents inhibit calcium ion passage through channels resulting from the expression of α_{1C}, α_{1D}, α_{1S}, or α_{1F} genes or any isoforms thereof (embodiments of the α_{1S} subunit are shown in SEQ ID Nos. 1 and 2; an embodiment of the α_{1C} subunit is shown in SEQ ID No. 3; an embodiment of the α_{1D} subunit is shown in SEQ ID No. 4; embodiments of the α_{1F} subunit are shown in SEQ ID Nos. 5-7). In one alternative of this embodiment, the agent is a member of the dihyropyridine class of compounds. Suitable dihydropyridine compounds are shown in Table Y.

TABLE Y

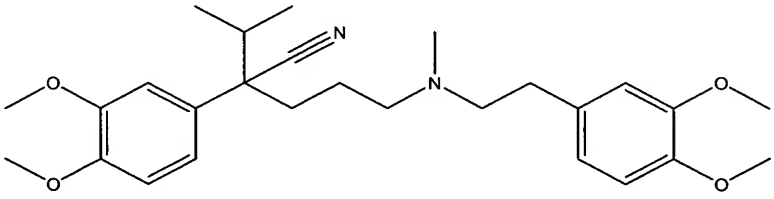
Common Name	Structure
Nimodipine	

Common Name	Structure
Nicardipine	
Nifedipine	
Amlodipine	
Isradipine	

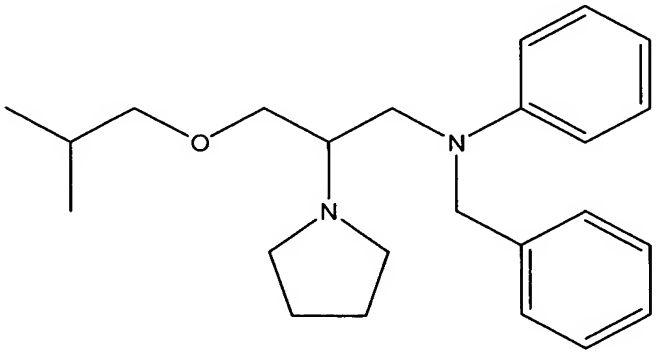
[0397] In another embodiment, agents belonging to the benzothiazepine class of compounds may be employed to inhibit passage of calcium ions through a L-type channel. By way of example, diltiazem, having the structure shown below, is a benzothiazepine suitable for use in the current invention.



[0398] In still another embodiment, agents belonging to the diphenylalkylamine class of compounds may be employed to inhibit passage of calcium ions through a L-type channel. By way of example, verapamil, having the structure shown below, is a diphenylalkylamine suitable for use in the current invention.



[0399] In yet another embodiment, bepridil may be employed to inhibit passage of calcium ions through a L-type channel. Bepridil has the following structure:



[0400] In still other embodiments, agents belonging to the piperidine class of compounds, such as those detailed in U.S. Patent No. 5,981,539, which is hereby

incorporated by reference in its entirety, may be employed to inhibit calcium ion flow through an L-type channel.

[0401] In a further alternative embodiment, the HVA gated channel is a N-type HVA channel. Generally speaking, these agents inhibit calcium ion passage through channels resulting from the expression of the α_{1B} gene or any isoforms thereof (an embodiment of the α_{1B} subunit is shown in SEQ ID No. 8). By way of example, suitable agents that inhibit the flow of calcium ions through an N-type channel include omega-conopeptides, such as ω-conotoxin GVIA (SEQ ID No:21) or ω-conotoxin MVIIA (SEQ ID No:22), which are components of peptide toxins produced by marine snails of the genus *Conus*. Other suitable omega-conopeptides are detailed in U.S. Patent No. 6,156,726, which is hereby incorporated by reference in its entirety. By way of further example, neomycin sulfate or ziconotide may be employed to inhibit the flow of calcium ions through an N-type channel.

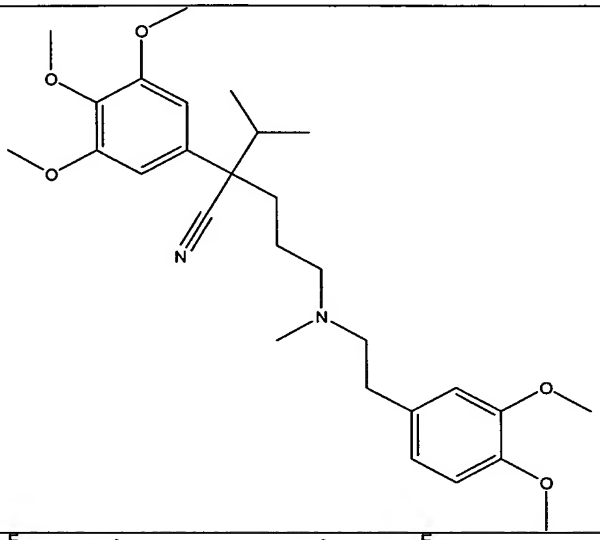
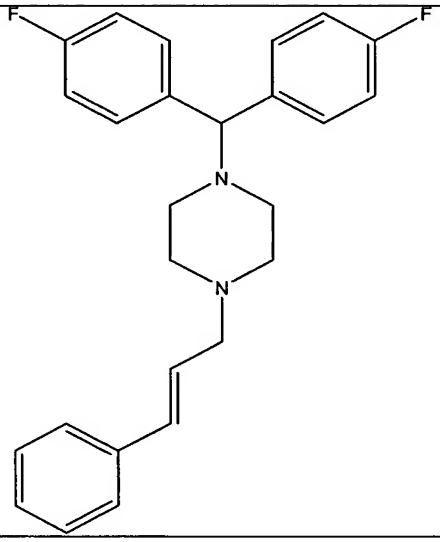
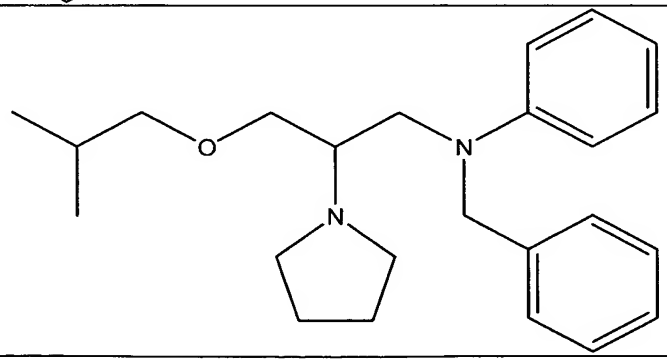
[0402] In still another alternative embodiment, the HVA gated channel a P/Q-type channel. Typically, these agents inhibit calcium ion passage through channels resulting from the expression of the α_{1A} gene or any isoforms thereof (embodiments of the α_{1A} subunit are shown in SEQ ID Nos. 9-11). Suitable agents that inhibit passage of calcium ions through a P/Q-type channel include certain isolates of funnel web spider toxin, such as agatoxin IVA (SEQ ID No:23) or agatoxin IIIA (SEQ ID No:24), and ω-conotoxin MVIIC (SEQ ID No:25).

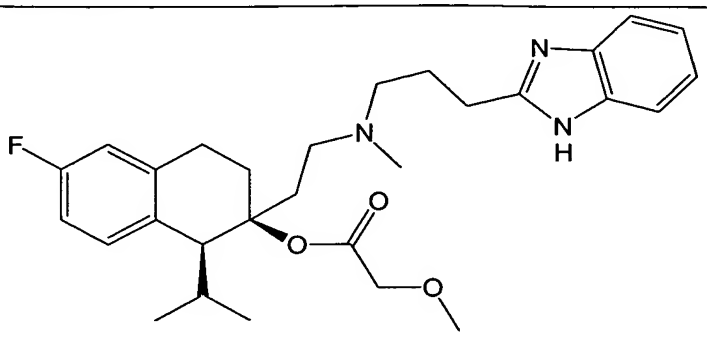
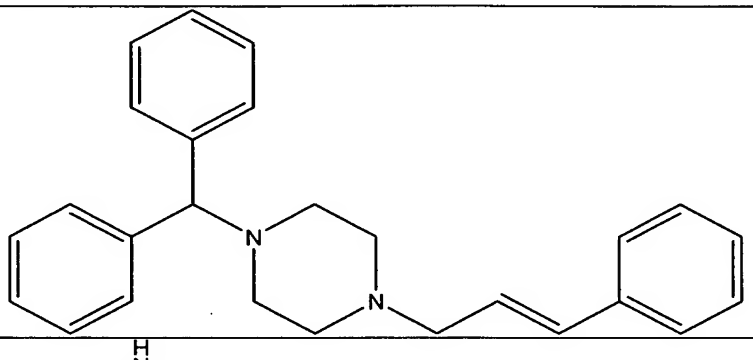
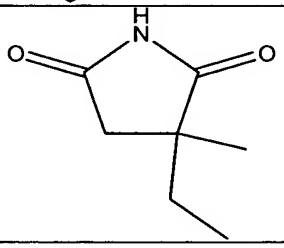
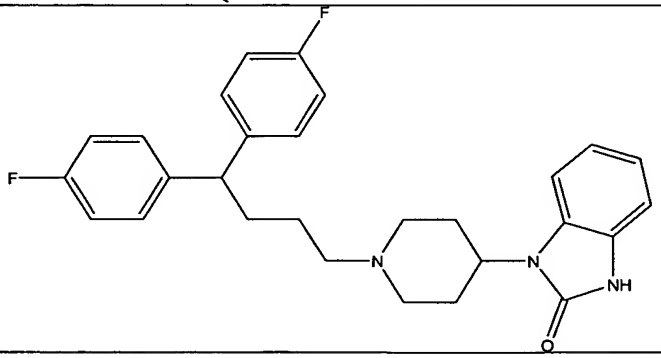
[0403] Yet a further alternative embodiment provides agents that inhibit calcium ion passage through a R-type HVA channel. In general, these agents inhibit calcium ion passage through channels resulting from the expression of the α_{1D} gene or any isoforms thereof (embodiments of the α_{1D} subunit are shown in SEQ ID Nos. 12-14). By way of example, SNX-482 (SEQ ID No:26), a 41 amino acid peptide isolated from the venom of the African tarantula *Hysterocrates gigas,* may be employed to inhibit the passage of calcium ions through an R-type channel.

[0404] Another embodiment encompasses agents that inhibit calcium ion passage through a LVA gated channel. In one alternative of this embodiment, the agent inhibits the passage of calcium ions through a T-type calcium channel. Generally speaking, these agents inhibit calcium ion passage through channels resulting from the expression of α_{1G}, α_{1H}, or α_{1L} genes or any isoforms thereof (embodiments of the α_{1G} subunit are shown in SEQ ID Nos. 15-18; embodiments of the α_{1H} subunit are shown in SEQ ID Nos. 19 and 20). In one

embodiment, agents belonging to the phenylalkylamine class of compounds, such as flunarizine or cinnarizine, may be employed to inhibit passage of calcium ions through a T-type channel. By way of example, a number of agents suitable for inhibiting the passage of calcium ions through a T-type channel are shown in Table X.

TABLE X

Common Name	Structure
Gallopamil	
Flunarizine	
Bepridil	

Common Name	Structure
Mibefradil	
Nickel Chloride	NiCl
Cinnarizine	
Ethosuximide	
Pimozide	

[0405] A further aspect of the invention encompasses calcium modulating agents that inhibit the intracellular passage of Ca^{2+} ions through a receptor operated calcium channel (ROC). Generally speaking, activation of a ROC opens a cation-selective channel that allows an influx of extracellular Ca^{2+} and Na^{+} resulting in an increase in intracellular Ca^{2+} concentration. In accordance with the practice of the invention, a number of calcium modulating agents may be employed to inhibit activation of a ROC. Typically, the agent is a ROC receptor antagonist or a derivative or analog of a calcium channel receptor antagonist.

[0406] In one embodiment, the ROC is a NMDA receptor-ionophore complex. Generally speaking, the activity of the NMDA receptor-ionophore complex is regulated by a variety of modulatory sites that can be targeted by selective antagonists. By way of example, competitive antagonists, such as the phosphonate AP5, act at the glutamate binding site, whereas noncompetitive antagonists, such as phencyclidine (PCP), MK-801 or magnesium (Mg^{2+}), act within the associated ion channel (ionophore). Alternatively, there is also a glycine binding site that can be blocked selectively with compounds such as 7-chlorokynurenic acid. By way of further example, other potential sites for modulation of NMDA receptor function include a zinc (Zn^{2+}) binding site and a sigma ligand binding site. Additionally, endogenous polyamines such as spermine bind to a specific site and so potentiate NMDA receptor function. A number of other suitable NMDA receptor antagonists are detailed in U.S. Patent No. 6,306,912, which is hereby incorporated by reference in its entirety.

[0407] In an alternative embodiment, the ROC is a calcium-permeable AMPA receptor. The activity of the AMPA receptor is regulated by a number of modulatory sites that can be targeted by selective antagonists. By way of example, quinoxalinediones are a potent class of competitive receptor antagonists that may be employed. By way of further example, GYKI 52466, a 2,3-benzodiazepine, a highly selective, noncompetitive antagonist of AMPA/kainate receptor responses may also be employed. Additionally, a number of other suitable AMPA receptor antagonists are detailed in U.S. Patent No. 6,306,912, which is hereby incorporated by reference in its entirety.

[0408] In still another alternative embodiment, the ROC is or a nicotinic cholinergic receptor. By way of example, passage of Ca^{2+} ions through a nicotinic cholinergic receptor may be inhibited by the arylalkylamine toxin, philanthotoxin. By way of further example, passage of Ca^{2+} ions through a nicotinic cholinergic receptor may be inhibited by mecamylamine. A number of other suitable nicotinic cholinergic receptor antagonists are detailed in U.S. Patent No. 6,306,912, which is hereby incorporated by reference in its entirety.

[0409] A further aspect of the invention encompasses calcium modulating agents that are calcium chelating agents. Generally speaking, calcium chelating agents suitable for use in the present invention include agents that attach to Ca^{2+} ions by coordinate links to two or more nonmetal atoms in the same molecule. In some aspects, the chelating agent binds extracellular Ca^{2+} ions and inhibits its intracellular passage. In other aspects, the chelating agent binds to intracellular Ca^{2+} ions and inhibits it from functioning as a secondary

messenger in response to a reduced blood flow to a central nervous system cell, such as resulting from an ischemic casacade or traumatic injury.

[0410] In one embodiment, the chelating agent comprises a compound having formula X

[0411] $(HOOC\text{-}CH_2\text{-})_2\text{-N-A-N-(-}CH_2\ COOH)_2$

[0412] wherein A is a saturated or unsaturated, aliphatic, aromatic or heterocyclic linking radical containing, in a direct chain link between the two depicted nitrogen atoms, 2-8 carbon atoms in a continuous chain which is interrupted by 2-4 oxygen atoms, provided that the chain members directly connected to the two depicted nitrogen atoms are not oxygen atoms and pharmaceutically acceptable salts of said carboxylic acids.

[0413] In a further embodiment for compounds having formula X, A is selected from the group consisting of saturated or unsaturated aliphatic chain interrupted by 2-4 oxygen atoms, and -CR=CR-O-CH_2CH_2-O-CR'=CR', where each of the pairs of radicals R-R and R'-R', together with the attached -C=C- moiety, complete an aromatic or heterocyclic ring containing 5 or 6 ring atoms, the ring completed by R-R being the same as or different from that completed by R'-R'. In a further alternative for this embodiment, the aromatic or heterocyclic ring completed by the pairs of radicals R-R and R'-R', together with the attached -C=C- moiety, is selected from the group consisting of furan, thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, oxazole, isoxazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, thiazole, isothiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, benzene, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, and 1,2-, 1,3- and 1,4-oxazines and -thiazines, the ring completed by R-R being the same as or different from the ring completed by R'-R'. In still a further alternative for this embodiment, the pairs of radicals R-R and R'-R', together with the attached -C=C- moiety, completes the same or different rings selected from unsubstituted and substituted benzene rings, in which substituted benzene rings contain 1-4 substituents selected from the group consisting of saturated or unsaturated $C_{1\text{-}4}$-alkyl, saturated or unsaturated $C_{1\text{-}4}$-alkoxy, fluorine, chlorine, bromine, iodine and CF_3, or a single divalent substituent which is -O-$(CH_2)_n$-O- and n is 1-3.

[0414] In a further embodiment for compounds having formula X, A is selected from the group consisting of -CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-, and -CH_2CH_2-(N(-CH_2COOH)-CH_2CH_2-)$_n$ wherein n is 1 to 5.

[0415] In still a further embodiment for compounds having formula X, the compound is selected from the group consisting of ethylene-1,2,-diol-bis-(2-aminoethyl

ether)-N,N,N',N'-tetraacetic acid (EGTA);1,2-bis-(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA), EDTA, and DTPA.

[0416] In yet another embodiment for compounds corresponding to formula X, the compound is a di or tetra ester of a compound having formula X. In one alternative of this embodiment, the compound is a neutral lipophillic ester of EDTA, DTPA, EGTA and BAPTA.

[0417] In another embodiment, the chelating agent comprises a compound having formula XI

[0418] $((HO)_2OP\text{-}CH_2\text{-})_2\text{-N-A-N-(-}CH_2\ PO(OH)_2)_2$

[0419] where A is saturated or unsaturated, aliphatic, aromatic or heterocyclic linking radical containing, in a direct chain link between the two depicted nitrogen atoms, 2-8 carbon atoms in a continuous chain which is interrupted by 2-4 oxygen atoms, provided that the chain members directly connected to the two depicted nitrogen atoms are not oxygen atoms and pharmaceutically acceptable salts of said phosphonic acids.

[0420] In a further embodiment for compounds having formula XI, A is selected from the group consisting of saturated or unsaturated aliphatic chain interrupted by 2-4 oxygen atoms, and -CR=CR-O-CH_2CH_2-O-CR'=CR', where each of the pairs of radicals R-R and R'-R', together with the attached -C=C- moiety, complete an aromatic or heterocyclic ring containing 5 or 6 ring atoms, the ring completed by R-R being the same as or different from the ring completed by R'-R'. In a further alternative for this embodiment, the aromatic or heterocyclic ring completed by the pairs of radicals R-R and R'-R', together with the attached -C=C- moiety, is selected from the group consisting of furan, thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, oxazole, isoxazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, thiazole, isothiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, benzene, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, and 1,2-, 1,3- and 1,4-oxazines and -thiazines, the ring completed by R-R being the same as or different from the ring completed by R'-R'. In still a further alternative for this embodiment, the pairs of radicals R-R and R'-R', together with the attached -C=C- moiety, complete the same or different rings selected from unsubstituted and substituted benzene rings, in which substituted benzene rings contain 1-4 substituents selected from the group consisting of saturated or unsaturated C_{1-4}-alkyl, saturated or unsaturated C_{1-4}-alkoxy, fluorine, chlorine, bromine, iodine and CF_3, or a single divalent substituent which is -O-$(CH_2)_n$-O- where n is1-3.

[0421] In a further embodiment for compounds having formula XI, A is selected from the group consisting of $-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-$, and $-CH_2CH_2-(N(-CH_2PO(OH)_2)-CH_2CH_2-)_n$,

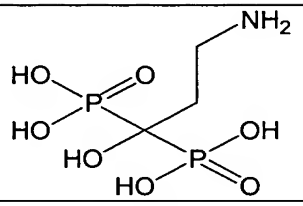
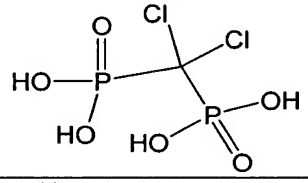
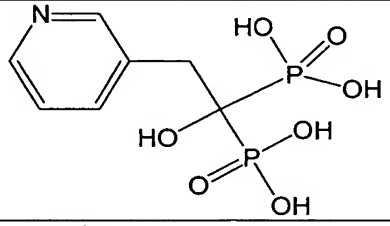
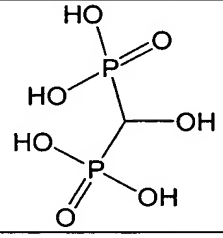
[0422] wherein n is 1 to 5.

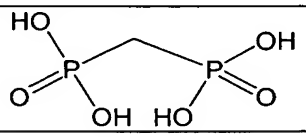
[0423] In still a further embodiment for compounds having formula XI, the compound is selected from the group consisting of ethylene-1,2,-diol-bis-(2-aminoethyl ether)-N,N,N',N'-tetramethylenephosphonic acid (EGTMP);1,2-bis-(2-aminophenoxy)ethane-N,N,N',N'- tetramethylenephosphonic acid (BAPTMP); EDTMP; and DTPMP.

[0424] In yet another embodiment for compounds corresponding to formula XI, the compound is a di or tetra ester of a compound having formula X. In one alternative of this embodiment, the compound is a neutral lipophillic ester of EGTMP, BAPTMP, EDTMP or DTPMP.

[0425] In still another embodiment, the calcium chelating agent is selected from the compounds listed in Table T.

TABLE T

Name	Structure
Pamidronic Acid	
Clodronic Acid	
Risedronic Acid	
Oxidronic Acid	

Name	Structure
Methylenediphosphonic Acid	

[0426] Examples of other suitable calcium modulating agents are detailed in Table V.

TABLE V

Common Name	Trade Name	Reference
A-53930A (isolated from the culture medium of Streptomyces vinaceusdrappus SANK 62394)		JP 08208690
AE-0047 Watanidipine dihydrochloride		EP 00424901
AGN-190604		Inflammation 1995, 19:2 (261-275)
AGN-190744		EP 372940 A2
AH-1058		European Journal of Pharmacology (2000), 398(1), 107-112
AHR 5360C		European Journal of Pharmacology (1988), 146(2-3), 215-22
AHR 12234		Archives Internationales de Pharmacodynamie et de Therapie (1989), 301: 131-50
AHR-12742		ZA 08604522

Common Name	Trade Name	Reference
AHR-16303B		Journal of Cardio vascular Pharmacology (1991 Jan), 17(1), 134-44
AHR-16462B		Drug Development Research (1991), 22(3), 259-71
AIT 110		
AIT 111		
AJ 2615		WO 8601203 A1
AJ-3941		Arzneimittel Forschung (1996 Jun), 46(6), 567-71
(+) alismol		JP 04077420 A2
AM-336 synthetic version of CVID marine cone snail venom	synthetic version of the natural omega-conotoxin	WO9954350
AM 543		
amlodipine	Norvasc	US 4572909
(S)-(-) amlodipine		GB 2233974 A1

Common Name	Trade Name	Reference
AN 132		EP 196648 A1
anipamil LU 42668		EP 64158 A1
antioquine (alkaloid from stem bark)		Journal of Natural Products (1992), 55(9), 1281-6
AP-1067		IDdb 268934
AQ-AH-208		CH 645628 A
AR 12456 (derivative of trapidil)		BE 902218 A1; Cardiovascular Drug Reviews (1991), 9(4), 385-97
aranidipine	Bec MPC1304 Sapresta	US 4446325
atosiban		EP 00112809
azelnidipine CS 905	Calblock	EP 88 266922
B 84439		EP 240828

Common Name	Trade Name	Reference
barnidipine (derivative of nicardipine)	Cyress, Hypoca, Mepirodipine, YM09730	US 4220649; DE 02904552
BAY-E-6927		DE 2117571
BAY-K-9320		EP 9206
BAY-T-7207		
BBR-2160		EP 282904 A2
BDF 8784		EP 25111
belfosdil BMY 21891 SR 7037		EP 173041 A1
bencyclane EGYT-201		FR 151193
benipidine KW3049, Nakadipine	Caritec, Coniel	US 4448964
bepridil	angopril, Bapadin, Bepricor, CERM1978, Cordium, OREG 5730, Vascor	US 3962238
bisaramil RGH 2957	Yutac	WO 9622096 A1

Common Name	Trade Name	Reference
BK 129		Methods and Findings in Experimental and Clinical Pharmacology (1992), 14(3), 175-81
BMS-181102		EP 559569
BMS-188107		US 5070088
BMY 20014		DE 3512995 A1
BMY 20064		DE 3512995 A1
BMY-43011		Bioorganic and Medicinal Chemistry Letters 1993, 3:12 (2817-2820)
BN 50149		WO 9323082 A1
BN 50175		WO 9323082 A1
BN 50394		WO 9323082 A1
BR 1022		Current Science (2002), 83(4), 426-431
BRL 3287A		WO 9323082 A1
BRL-32872		WO 09323024

Common Name	Trade Name	Reference
buflomedil		US 4326083
butoprozine		DE 2707048
CAF 603		Organic and Bio-Organic Chemistry (1994), (22), 3349-52
calciseptine (venom poly peptide)		WO 2000 069900
calcium antagonists		WO 9205165 A1
calcium channel antagonists		WO 00236586; WO 0236567 A1
calcium channel blocker (L-type)		Journal of Medicinal Chemistry (1996), 39(15), 2922-2938
calcium channel blockers		EP 400665 A2; US 4965356
calcium channel blockers		WO 9526325
carvedilol	Artist, Aucardic, BM14190, Cardiol, Carloc, Caslot, Coreg, Coropres, Dilatrend, Dilbloc, Dimitone, DQ2466, Eucardic, Kredex	US 4503067

Common Name	Trade Name	Reference
caryachine		British Journal of Pharmacology (1995 Dec), 116 (8), 3211-8
CD-349		EP 92936 A1
CD-832		EP 00370821
CER-2 metabolite of furnipidine	1E 7M	WO 9919302
cerebrocrast		DE 3534385 A1
CERM 11956		EP 138684 A2
CERM-12816		IDdb 283075
CGP 22442		WO 9323082
CGP 26797		WO 9323082
CGP 28727		WO
CGP 32413		WO 9323082
changrolin		Sci. Sin. (Engl. Ed.) (1979), 22 (10), 1220-8

Common Name	Trade Name	Reference
CHF-1521 (combination of delapril & manidipine)		
cilnidipine	Atelec, Cinalong, FRG 8653, Siscard	US 4672068
cinnarizine 516-MD	Stugeron Cinnaron	US 3799934
civamide	cis-capsaicin	WO 9640079; US 5840762
clentiazem, TA 3090	Logna	EP 00127882; US 4567175
clevidipine		WO 9512578
CNS-1067		IDdb 211675
CNS-1237		Annals of the New York Academy of Sciences (1995), 765 (Neuroprotective Agents), 210-29
CNS-2103 (from spider venom)		WO 9214709 A2

Common Name	Trade Name	Reference
COR 28-22		WO 9323082
COR 2707C		WO 9323082
COR 3752C		WO 9323082
CP-060S		WO 9500471 A1
CPC-301		IDdb 231888
CPC 304		IDdb 185705
CPC-317		IDdb 185700
CPU 23		Yaoxue Xuebao (1990), 25(11), 815-23. CAN 114:143097
CPU-86017		EP 00538844
CRE 202		WO 9323082
CRE 204		WO 9323082
CRE 1005		WO 9323082

Common Name	Trade Name	Reference
CRL-42752		WO 00003987
cronidipine LF 2-0254		EP 240398 A1
CV 159		FR 2511370 A1
D-2024 see verapamil(S)		WO 09509150
D 2603		WO 9323082
dagapamil		WO 9323082; EP 64158 A1
darodipine PY 108068		EP 00000150
dauricine NSC 36413		Chung-Kuo Yao Li Hsueh Pao (Acta Pharmacologica Sinica) (1986 Nov), 7(6), 543-7
des methyl verapamil		
DHM 9		WO 8604581 A1
DHP-218 PAK 9		EP 00121117
diclofurime		DE 79-2922799
dihydropyridine calcium channel blockers		Journal of Medicinal Chemistry (1998), 41(4), 509-514

Common Name	Trade Name	Reference
diltiazem	Cardizem, Dilacor, Tiazac	US 3562257
diperdipine		EP 00218996
dipfluzine		DE 3318577 A1
diproteverine BRL 40015		BE 866208
dopropidil		EP 00031771
dotarizine FI 6026	Dotaricin,	US 4883797
DTZ-323		Molecular Pharmacology (1997), 51(2), 262-268
E-2050		JP 2001199949 A2
E 4080		EP 344577 A2
efonidipine hydrochloride	Landel, NZ105, Selefodipine	US 4885284

Common Name	Trade Name	Reference
EG 1088		EP 56637 A1
EGIS 3966		DE 4027052 A1
elgodipine		DE 3825962 A1
emopamil (racemic) SZ 45		DE 3344755 A1
(S)-emopamil		DE 3344755 A1
enalapril + nitrendipine, Vita-Invest		EP 00884054
etafenone LG 11457	Baxacor	DE 1265758
ethosuximide	Suxinutin, Zardondan, Zardontin	
eugenodilol		JP 11255719 A2
evodiamine		JP 52077098
F-0401		EP 00320984

Common Name	Trade Name	Reference
falipamil AQA 39		Journal of Medicinal Chemistry (1990 May), 33 (5), 1496-504
fantofarone SR 33557		EP 235111 A1; US 4957925
fasudil (iv formulation), Asahi	Erik, Fasdil, AT877	US 4678783
FCE-24265		EP 373645 A1
FCE-26262		
FCE-27335		
FCE-27892		
FCE-28718		EP 00755931
fedopamil		
felodipine	Lexxel Plendil	US 4264611
felodipine + ramipril, Astra/Aventis		WO 09607400
fendiline	Sensit Cordan (HCl)	US 3262977
feniline		

Common Name	Trade Name	Reference
flezelastine, D 18024		EP 590551 A2
flordipine		
flunarizine	Sibelium	US 3773939
fluodipine		Arzneimittel-Forschung (1992), 42(11), 1284-7
fluphenazine, S94; SQ 4918; Triflumethazine; Vespazine	Elinol, Pacinol, Siqualon, Valamina	JOURNAL OF MEDICINAL CHEMISTRY (1976 Jun), 19(6), 850-2
fostedil KB944		EP 10120
FPL 62129		EP 125803 A2
FR 46171		
FR-172516		JP 09040647 A2
FRC 8411		
FRG 8653		
FRG-8701		
furaldipine		
furnidipine (CRE 319)		Journal of Medicinal Chemistry (1995 Jul 21), 38 (15), 2830-41
gallopamil (methoxy analog of verapamil)	Procurum	US 3262977
GOE 5057		
GOE 5584A		EP 173933 A1
GOE 93007		
GR 60139		
GR 66234A R-enantiomer of telupidine		Haematologica (1994), 79(4), 328-33

Common Name	Trade Name	Reference
GR 66235A, L-enantiomer of telupidine		Haematologica (1994), 79(4), 328-33
GS-386		
GYKI 46544		
H 32438		
HA 22		US 5240947 A
HA 23		US 5240947
HA 1004		
HA 1077		
HE 30346		
HNS 32		JP 08311007 A2
HOE 166		Molecular Pharmacology (1988 Apr), 33(4), 363-9
HOE 263		
HP 406		US 4521537
ICI 206970		EP 293170 A1 19881130
iganidipine		JP 63225355 A2 19880920
IHC 72		YAO HSUEH HSUEH PAO [ACTA PHARMACEUTICA SINICA] (1992), 27(6), 407-11
ipenoxazone		

Common Name	Trade Name	Reference
isradipine	Dynacirc	US 4466972
JTV-519	K-201	WO 09212148
KB 2796		
KP-840		Yakubutsu, Seishin, Kodo (1992), 12(6), 353
KP 873		
KT-362		ARCHIV DER PHARMAZIE (1995 Apr), 328(4), 313-6
KT 2230		GENERAL PHARMACOLOGY (1991), 22(3), 443-8
KW 3049 (see benipidine)		
L-366682		EP 00444898
L-651582		
L 735821		WO 9514471 A1 19950601 British Journal of Pharmacology (2001), 132 (1), 101-110

Common Name	Trade Name	Reference
lacidipine GR43659 SN305	Aponil, Caldine, Lacimen, Lacipil, Midotens, Motens, Viapress	US 4801599; DE 03529997
LAS 30356		
LAS 30398		
LAS-30538		Journal of Pharmacy and Pharmacology (1992 Oct), 44(10), 830-5
LAS Z077		
LCB-2514		
lemildipine		P 59152373 A2
lercanidipine	Cardiovasc, Carmen, Coifeo, Lercadip, Lerdip, Lerzam, REC152375, Vasodip, Zanedip, Zanidip	US 4705797
leualacin		EP 00358418
levosemotiadil, SA 3212		WO 08700838
lidoflazine R7904	Clinium	US 3267104
lifarizine RS 87476		US 04935417
LOE-908		

Common Name	Trade Name	Reference
lomerizine KB 2796	Migsis	US 4663325; EP 00159566
LU 49700 (main metabolite of galllopamil)		DE 3642331 A1
LU 49938		
LY-042826		European Journal of Pharmacology (2000), 408(3), 241-248
LY-393615		European Journal of Pharmacology (2000), 408(3), 241-248
manidipine CV 4093, franidipine	Calslot, Iperten, Manivasc	US 4892875; EP 00094159
MCI 176 (MY7674)		EP 169537 A2
McN 5691 (see RWJ 26240		
McN-6186		
MCN 6497		
MD 260792		
MDL 143		
MDL 12330A		
MDL 16582A		WO 9323082
MDL 72567		GB 2137622 A1 19841010 CAN 102:95549

Common Name	Trade Name	Reference
MEM 1003 nimopidine analog BAY Z 4406		
mepirodipine		
mesudipine		
mibefradil	Posicor	EP 00268148; US 4808605
minodipine		
mioflazine		
MJ 14712		
monatepil maleate (AD 2615)		WO 08601203; US 4749703
MPC 1304		
MPC 2101		FR 2514761 A1
MR-14134		Pharmacology (1995), 51 (2), 84-95
N-3601		EP 254322 A1
N 20776		
N-allyl secoboldine		
naltiazem Ro 23-6152		US 4652561
NB 818		
NC 1100		
NC O 700		
NCC 09-0026		
nexopamil		EP 00271013
NH 2250		
NH 2716		

Common Name	Trade Name	Reference
nicainoprol RU 42924		DE 2934609
nicardipine nifelan	Cardene	US 3985847
nictiazem		
nifedipine	Procardia Adalat EnSo Trol	US 3485847
nigulipine		WO 8807525 A1
niludipine		
nilvadipine FK 235	Escor Nivadil	US 4338322 DE 02940833
nimodipine	Nimotop	US 3842096
nisoldipine Bay y 5552	Sular Sysdor	US 4154839
nitrendipine Bay k 5009	Baypress	US 3799934
NMDA/calcium channel antagonists, Allelix		WO 09745115
NKY 722		

Common Name	Trade Name	Reference
NMED 126 (MC-34D)		WO 0145709 A1; US 6387897
NMED 427		WO 0145709 A1; US 6387897
NMED 724		WO 0145709 A1; US 6387897
NMED 826		WO 0145709 A1; US 6387897
NMED JM-G-10		WO 0145709 A1; US 6387897
NMED 157 39-1B4		WO 0145709 A1; US 6387897
NMED 160 39-45-3		WO 0145709 A1; US 6387897
NNC-09-0026		WO 9201672
NP 252		Life Sciences (1991), 48(2), 183-8
NS 626		
NS-638		US 5314903; EP 545845 A1

Common Name	Trade Name	Reference
NS-649		EP 520200 A2
NS-696		
NS-7		WO 09607641
NS 3034		
NZ 105		
olradipine S 11568		FR 2602231 A1
ONO-2921		WO 0000470 A1
OPC 13340		
OPC 88117		EP 236140 A2
ORG 13020		
Org-13061		Fundamental & Clinical Pharmacology (1997), 11(5), 416-426
OSAT (nifedipine)		
osthole	Osthol	JP 47000430
oxodipine, IQB 837V		ES 531033 A1
P 0825		
P 1268		
palonidipine hydrochloride		EP 128010 A2
PCA-50922		

Common Name	Trade Name	Reference
PCA-50938		Brain Research (1997), 772 (1,2), 57-62
PCA-50941		
PCA 50982		
PD-0204318		WO 9943658 A1
PD-029361		IDdb 300520
PD 122860		EP 206747 A2
PD 151307		US 6423689; J. Med. Chem (43), 3474, 2000
PD-157667		US 5767129
PD-158143		WO 9705125 A1
PD 173212		
PD 175069		WO 9854123 A1
PD-176078		WO9955688; J. Med. Chem (43), 3474, 2000
PD 181283		Bioorganic & Medicinal Chemistry Letters (1999), 9(16), 2453-2458
pelanserin		
perhexiline	Pexid	GB 1025578
petrosynol		Tetrahedron (1993), 49(45), 10435-8
PF 244		
PFS 1144 (EO 122)		DE 2802208

Common Name	Trade Name	Reference
pirmenol	Pirmavar, Pimenol, CI845	US 4112103
pirprofurol		
pimozide		Journal of Neuroscience (2002), 22(2), 396-403.
PN 200110		
PNU 156654E		WO 9705102 A1
pranidipine OPC 13340	Acalas	EP 00145434
prenylamine	Angormin	US 3152173
propiverine	Detrunorm, Mictonorm, Mictonetten, BUP 4	DD 106643
ptilomycalin AM	mimic of ptilomycalin	
QM 96233		
QM 96159		
QM 96127		
QX-314		Biophysical Journal (1979 Jul), 27(1), 39-55.

Common Name	Trade Name	Reference
R 56865		EP 184257 A1
R 59494		EP 184257 A1
R 71811		
Rec 152288		
Rec 152375 Rec 15/375		
RGH-2716 (TDN 345)		EP 414421 A2
RGH 2970		
riodipine		
Ro-11-2933		EP 00523493
Ro 18-3981		
Ro 40-5967		
RO 445912 dithaine derivatives of tiapamil		Biochemical Pharmacology (1995), 50(2), 187-96
ronipamil		
RS-5773		EP 00353032
RS 93007		
RS 93522		US 4595690
RU-43945		WO 9323082 A1
RWJ-22108		US 04845225
RWJ-22726		US 04845225
RWJ 26240 McN 5691		EP 146271 A2

Common Name	Trade Name	Reference
RWJ 26899		EP 237191 A1
RWJ-26902		
RWJ-29009		EP 00493048
RWJ-37868		WO 0048584 A2
ryanodine		
S-(-)-amlodipine		
S 11568		
S 12967		ZA 9000231 A
S-12968		EP 00406502
S-2150		EP 00615971
S-312-d		JP 03052890
S 830327		
SA 2572		JP 63104969 A2
SA 2995		
SA 3212		
sabeluzole		EP 184257 A1
safinamide	FCE 26743, NW 1015, PNU 151774	EP 400495 A1
sagandipine		

Common Name	Trade Name	Reference
salicylaldoxime		Clinical and Experimental Pharmacology and Physiology (1999 Dec), 26 (12), 964-9
SANK-71996		
SB-201823A		WO 09202502
SB-206284A		
SB 221420A		WO 9602494 A1
SB-237376		WO 0209761 A2
SB 262470	NPS 2143	WO 0183546 A1
SC 30552		
SDZ-249482		
selodipine		
semotiadil (SD 3211)		US 4786635; JP 09012576
SIM 6080		EP 293925 A2
sipatrigine		EP 372934 A2
sinomenine (active from a Chinese medicinal plant)		WO 0269971 A1
siratiazem		WO 09117153
SKF-45675		

Common Name	Trade Name	Reference
SKF-96365		European Journal of Pharmacology (1990 Jun 12), 188(6), 417-21
SKT-M-26		
SL-34.0829		WO 0209761 A2
SL 651708		
SL 851016		
SL-870495		
SM-6586		EP 00177965
SNX-124		
SNX 185	w-Conotoxin G VIA	WO 9310145 A1
SNX-236		WO 09313128
SNX-239		Pain (1995), 60(1), 83-90
SNX-482, peptides from tarantula venom		WO 9805780 A2
sornidipine		
SQ 31486		EP 205334 A2
SQ-31727		
SQ 31765		
SQ 32321		

Common Name	Trade Name	Reference
SQ 32324		
SQ 32547		EP 400665 A2
SQ 32926		EP 400665 A2
SQ-33351		WO 09006118
SQ 33537		
SQ-34399		
SR-33805		EP 576347 A1
SUN 5647		
SUN 6087		
SUN-N8075		WO 9923072 A1
T-477		EP 00441539
TA-993		JP 01050872
taludipine		
tamolarizine		EP 00354068
TDN-345		
Teczem		
temiverine	Urespan, NS 21	CAN 131:193592
terflavoxate		EP 72620 A1
terodiline TD 758	Bicor	US 3371014

Common Name	Trade Name	Reference
tetrandrine		Clinical and Experimental Pharmacology and Physiology (1996), 23(8), 751-753
TH-1177		
TH-9229		WO 09607415
thapsigargin		British Journal of Pharmacology (1985 Jul), 85(3), 705-12
tiapamil		
tinctormine		Chemical & Pharmaceutical Bulletin (1992), 40 (12), 3355-7
TJN 220 O-Ethylfangchinoline		JP 63179878 A2
TMB 8		Journal of Cell Science (1985 Nov), 79 151-60
TN-871		European Journal of Pharmacology (1998), 342(2/3), 167-175
TR 2957		
trapidil		
trimetazidine	Adexor, Idaptan, Preductal, S 5016, Trimetazine, Vastarel	US 3262852
TY-10835		Pharmacometrics 1998, 54:3 (153)

Common Name	Trade Name	Reference
U-88999		WO 9204338
U-92032		WO 09204338
U-92798		WO 9204338 A1
UK 1745		EP 653426 A1
UK-51656		EP 00089167
UK 52831		JP 59118782 A2
UK-55444		EP 00132375
UK 56593		
UK-84149		EP 404359 A1
ULAH 99		European Journal of Pharmacology (1992 Dec 8), 229(1), 55-62
vantanipidine	Calbren	EP 257616 A2
verapamil, verelan	Calan, Covera, Isopin Verelan	US 3261859
S-verapamil D-2024 levoverapamil		WO 09509150

Common Name	Trade Name	Reference
vexibinol Sophoraflavanone G		Chemical and Pharmaceutical Bulletin (1990 Apr), 38(4), 1039-44
vinigrol		
vintoperol RGH 2981 RT 303		WO 9207851
VUF-8929		EP 467435 A2
VULM 993		
vantanipidine	Calbren	EP 257616 A2
W 787		
WAS 4206		
WK 269		
WY 27569		
WY 44644		
WY 44705		
WY 46622		
WY 47324		
xanthonolol		US 5495005
Y 19638		
Y-22516		WO 9323082
Y 208835		
YC 114		
YH-334		EP 00366548
YM 15430-1 (see YM 430)		
YM-16151-4 (YM 151)		EP 00167371

Common Name	Trade Name	Reference
YM-430 (YM 15430)		WO 0209761 A2
YS 035		BE 897244 A2
YS 161		
Z-6568		Journal of Mass Spectrometry (1996), 31(1), 37-46
ziconotide omega connotoxin MVIIA SNX-111	Prialt, CI 1009, SNX 194	WO 9107980
ZM-224832		EP 00343865
zonisamide	Excegran, Zonegran	US 4172896

[0427] Generally speaking, the pharmacokinetics of the particular agent to be administered will dictate the most preferred method of administration and dosing regiment. The calcium modulating agent can be administered as a pharmaceutical composition with or without a carrier. The terms "pharmaceutically acceptable carrier" or a "carrier" refer to any generally acceptable excipient or drug delivery composition that is relatively inert and non-toxic. Exemplary carriers include sterile water, salt solutions (such as Ringer's solution), alcohols, gelatin, talc, viscous paraffin, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, calcium carbonate, carbohydrates (such as lactose, sucrose, dextrose, mannose, albumin, starch, cellulose, silica gel, polyethylene glycol (PEG), dried skim milk, rice flour, magnesium stearate, and the like. Suitable formulations and additional carriers are described in Remington's Pharmaceutical Sciences, (17.sup.th Ed., Mack Pub. Co., Easton, Pa.). Such preparations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants,

preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, preservatives and/or aromatic substances and the like which do not deleteriously react with the active compounds. Typical preservatives can include, potassium sorbate, sodium metabisulfite, methyl paraben, propyl paraben, thimerosal, etc. The compositions can also be combined where desired with other active substances, e.g., enzyme inhibitors, to reduce metabolic degradation.

[0428] Moreover, the calcium modulating agent can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The method of administration can dictate how the composition will be formulated. For example, the composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, or magnesium carbonate.

[0429] In another embodiment, the calcium modulating agent can be administered intravenously, parenterally, intramuscular, subcutaneously, orally, nasally, topically, by inhalation, by implant, by injection, or by suppository. For enteral or mucosal application (including via oral and nasal mucosa), particularly suitable are tablets, liquids, drops, suppositories or capsules. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Liposomes, microspheres, and microcapsules are available and can be used. Pulmonary administration can be accomplished, for example, using any of various delivery devices known in the art such as an inhaler. See. e.g. S. P. Newman (1984) in Aerosols and the Lung, Clarke and Davis (eds.), Butterworths, London, England, pp. 197-224; PCT Publication No. WO 92/16192; PCT Publication No. WO 91/08760. For parenteral application, particularly suitable are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. In particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-polyoxypropylene block polymers, and the like.

[0430] The actual effective amounts of compound or drug can and will vary according to the specific composition being utilized, the mode of administration and the age, weight and condition of the subject. By way of example, as used herein, an effective amount of the calcium modulating agent is an amount that achieves the desired degree of inhibition of Ca^{2+} ion flow down the electrochemical gradient of one or more calcium channels. Dosages for a particular individual subject can be determined by one of ordinary skill in the art using

conventional considerations. But in general, the amount of calcium modulating agent will be between about 10 to about 2500 milligrams per day. The daily dose can be administered in one to four doses per day.

[0431] In one embodiment, when the calcium modulating agent comprises nimodipine, typically the amount administered is within a range of from about 0.5 to about 500 milligrams per day, and even more typically, between about 40 to about 240 milligrams per day.

[0432] In another embodiment, when the calcium modulating agent is flunarizine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 1 to about 10 milligrams per day.

[0433] In yet another embodiment, when the calcium modulating agent is bepridil, generally the amount administered is within a range of from about 0.5 to about 500 milligrams per day, and even more typically, between about 200 to about 400 milligrams per day.

[0434] In still another embodiment, when the calcium modulating agent is diltiazem, typically the amount administered is within a range of from about 0.5 to about 50 milligrams per hour, and even more typically, between about 5 to about 15 milligrams per hour.

[0435] In yet a further embodiment, when the calcium modulating agent is felodipine, typically the amount administered is within a range of from about 0.5 to about 50 milligrams per day, and even more typically, between about 5 to about 20 milligrams per day.

[0436] In still another embodiment, when the calcium modulating agent is isradipine, typically the amount administered is within a range of from about 0.5 to about 50 milligrams per day, and even more typically, between about 2.5 to about 20 milligrams per day.

[0437] In yet another embodiment, when the calcium modulating agent is nicardipine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per hour, and even more typically, between about 20 to about 40 milligrams per hour.

[0438] In yet a further embodiment, when the calcium modulating agent is nifedipine, typically the amount administered is within a range of from about 0.5 to about 500 milligrams per day, and even more typically, between about 30 to about 120 milligrams per day.

[0439] In still another embodiment, when the calcium modulating agent is verapamil, typically the amount administered is within a range of from about 0.5 to about 1000 milligrams per day, and even more typically, between about 180 to about 540 milligrams per day.

[0440] In one embodiment, when the calcium modulating agent comprises lacidipine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 1 to about 10 milligrams per day.

[0441] In another embodiment, when the calcium modulating agent is lomerizine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 1 to about 20 milligrams per day.

[0442] In yet another embodiment, when the calcium modulating agent is propiverine, generally the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 15 to about 60 milligrams per day.

[0443] In still another embodiment, when the calcium modulating agent is trimetazidine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 20 to about 60 milligrams per day.

[0444] In yet a further embodiment, when the calcium modulating agent is zonisamide, typically the amount administered is within a range of from about 0.5 to about 1000 milligrams per day, and even more typically, between about 100 to about 600 milligrams per day.

[0445] In still another embodiment, when the calcium modulating agent is lercanidipine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 10 to about 20 milligrams per day.

[0446] In still another embodiment, when the calcium modulating agent is nilvadipine, typically the amount administered is within a range of from about 0.5 to about 50 milligrams per hour, and even more typically, between about 4 to about 16 milligrams per hour.

[0447] In yet a further embodiment, when the calcium modulating agent is benidipine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 2 to about 20 milligrams per day.

[0448] In still another embodiment, when the calcium modulating agent is nisoldipine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 10 to about 20 milligrams per day.

[0449] In one embodiment, when the calcium modulating agent comprises nitrendipine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 10 to about 40 milligrams per day.

[0450] In another embodiment, when the calcium modulating agent is manidipine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 10 to about 20 milligrams per day.

[0451] In yet another embodiment, when the calcium modulating agent is barnidipine, generally the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 10 to about 30 milligrams per day.

[0452] In still another embodiment, when the calcium modulating agent is efonidipine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 20 to about 40 milligrams per day.

[0453] In yet a further embodiment, when the calcium modulating agent is amlodipine, typically the amount administered is within a range of from about 0.5 to about 50 milligrams per day, and even more typically, between about 5 to about 10 milligrams per day.

[0454] In still another embodiment, when the calcium modulating agent is cilnidipine, typically the amount administered is within a range of from about 0.5 to about 50 milligrams per day, and even more typically, between about 5 to about 20 milligrams per day.

[0455] In still another embodiment, when the calcium modulating agent is lercanidipine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per hour, and even more typically, between about 10 to about 30 milligrams per hour.

[0456] In yet a further embodiment, when the calcium modulating agent is aranidipine, typically the amount administered is within a range of from about 0.5 to about 100 milligrams per day, and even more typically, between about 1.25 to about 20 milligrams per day.

[0457] In yet a further embodiment, when the calcium modulating agent is mibefradil, typically the amount administered is within a range of from about 0.5 to about 500 milligrams per day, and even more typically, between about 10 to about 100 milligrams per day.

[0458] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

[0459] Generally speaking, the calcium modulating agent and cyclooxygenase-2 selective inhibitor are administered to the subject as soon as possible after the reduction in blood flow to the central nervous system in order to reduce the extent of ischemic damage. Typically, the calcium modulating agent and cyclooxygenase-2 selective inhibitor are administered within 10 days after the reduction of blood flow to the central nervous system and more typically, within 24 hours. In still another embodiment, the calcium modulating agent and cyclooxygenase-2 selective inhibitor are administered from about 1 to about 12 hours after the reduction in blood flow to the central nervous system. In another embodiment, the calcium modulating agent and cyclooxygenase-2 selective inhibitor are administered in less than about 6 hours after the reduction in blood flow to the central nervous system. In still another embodiment, the calcium modulating agent and cyclooxygenase-2 selective inhibitor are administered in less than about 4 hours after the reduction in blood flow to the central nervous system. In yet a further embodiment, the calcium modulating agent and cyclooxygenase-2 selective inhibitor are administered in less than about 2 hours after the reduction in blood flow to the central nervous system.

[0460] Moreover, the timing of the administration of the cyclooxygenase-2 selective inhibitor in relation to the administration of the calcium modulating agent may also vary from subject to subject. In one embodiment, the cyclooxygenase-2 selective inhibitor and calcium modulating agent may be administered substantially simultaneously, meaning that both agents may be administered to the subject at approximately the same time. For example, the cyclooxygenase-2 selective is administered during a continuous period beginning on the same day as the beginning of the calcium modulating agent and extending to a period after the end of the calcium modulating agent. Alternatively, the cyclooxygenase-2 selective inhibitor and calcium modulating agent may be administered sequentially, meaning that they are administered at separate times during separate treatments. In one

embodiment, for example, the cyclooxygenase-2 selective inhibitor is administered during a continuous period beginning prior to administration of the calcium modulating agent and ending after administration of the calcium modulating agent. Of course, it is also possible that the cyclooxygenase-2 selective inhibitor may be administered either more or less frequently than the calcium modulating agent. Moreover, it will be apparent to those skilled in the art that it is possible, and perhaps desirable, to combine various times and methods of administration in the practice of the present invention.

COMBINATION THERAPIES

[0461] Generally speaking, it is contemplated that the composition employed in the practice of the invention may include one or more of any of the cyclooxygenase-2 selective inhibitors detailed above in combination with one or more of any of the calcium modulating agents detailed above. By way of a non limiting example, Table 4 details a number of suitable combinations that are useful in the methods and compositions of the current invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors or calcium modulating agents listed in Table 4.

TABLE 4

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound having formula I	nimodipine
a compound having formula I	nicardipine
a compound having formula I	nifedipine
a compound having formula I	amolodipine
a compound having formula I	isradipine
a compound having formula I	diltiazem
a compound having formula I	verapamil
a compound having formula I	bepridil
a compound having formula I	gallopamil
a compound having formula I	flunarizine
a compound having formula I	pimozide
a compound having formula II	nimodipine
a compound having formula II	nicardipine
a compound having formula II	nifedipine
a compound having formula II	amolodipine
a compound having formula II	isradipine
a compound having formula II	diltiazem
a compound having formula II	verapamil
a compound having formula II	bepridil
a compound having formula II	gallopamil
a compound having formula II	flunarizine
a compound having formula II	pimozide
a compound having formula III	nimodipine
a compound having formula III	nicardipine
a compound having formula III	nifedipine
a compound having formula III	amolodipine
a compound having formula III	isradipine
a compound having formula III	diltiazem
a compound having formula III	verapamil
a compound having formula III	bepridil
a compound having formula III	gallopamil
a compound having formula III	flunarizine
a compound having formula III	pimozide
a compound having formula IV	nimodipine
a compound having formula IV	nicardipine
a compound having formula IV	nifedipine
a compound having formula IV	amolodipine
a compound having formula IV	isradipine
a compound having formula IV	diltiazem
a compound having formula IV	verapamil
a compound having formula IV	bepridil
a compound having formula IV	gallopamil
a compound having formula IV	flunarizine
a compound having formula IV	pimozide
a compound having formula V	nimodipine
a compound having formula V	nicardipine

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound having formula V	nifedipine
a compound having formula V	amolodipine
a compound having formula V	isradipine
a compound having formula V	diltiazem
a compound having formula V	verapamil
a compound having formula V	bepridil
a compound having formula V	gallopamil
a compound having formula V	flunarizine
a compound having formula V	pimozide

[0462] By way of further example, Table 5 details a number of suitable combinations that may be employed in the methods and compositions of the present invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors or calcium modulating agents listed in Table 5.

TABLE 5

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	nimodipine

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	nicardipine

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	nifedipine

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	amolodipine

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	isradipine

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	diltiazem

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	verapamil

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	bepridil

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	gallopamil

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	flunarizine

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	pimozide

[0463] By way of yet further example, Table 6 details additional suitable combinations that may be employed in the methods and compositions of the current invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors or calcium modulating agents listed in Table 6.

TABLE 6

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
Celecoxib	nimodipine
Celecoxib	nicardipine
Celecoxib	nifedipine
Celecoxib	amolodipine
Celecoxib	isradipine
Celecoxib	diltiazem
Celecoxib	verapamil
Celecoxib	bepridil
Celecoxib	gallopamil
Celecoxib	flunarizine
Celecoxib	pimozide
Deracoxib	nimodipine
Deracoxib	nicardipine
Deracoxib	nifedipine
Deracoxib	amolodipine
Deracoxib	isradipine
Deracoxib	diltiazem
Deracoxib	verapamil
Deracoxib	bepridil
Deracoxib	gallopamil
Deracoxib	flunarizine
Deracoxib	pimozide
Valdecoxib	nimodipine
Valdecoxib	nicardipine
Valdecoxib	nifedipine
Valdecoxib	amolodipine
Valdecoxib	isradipine
Valdecoxib	diltiazem
Valdecoxib	verapamil
Valdecoxib	bepridil
Valdecoxib	gallopamil
Valdecoxib	flunarizine
Valdecoxib	pimozide
Rofecoxib	nimodipine
Rofecoxib	nicardipine
Rofecoxib	nifedipine
Rofecoxib	amolodipine
Rofecoxib	isradipine
Rofecoxib	diltiazem
Rofecoxib	verapamil
Rofecoxib	bepridil
Rofecoxib	gallopamil
Rofecoxib	flunarizine
Rofecoxib	pimozide
Etoricoxib	nimodipine
Etoricoxib	nicardipine

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
Etoricoxib	nifedipine
Etoricoxib	amolodipine
Etoricoxib	isradipine
Etoricoxib	diltiazem
Etoricoxib	verapamil
Etoricoxib	bepridil
Etoricoxib	gallopamil
Etoricoxib	flunarizine
Etoricoxib	pimozide
Meloxicam	nimodipine
Meloxicam	nicardipine
Meloxicam	nifedipine
Meloxicam	amolodipine
Meloxicam	isradipine
Meloxicam	diltiazem
Meloxicam	verapamil
Meloxicam	bepridil
Meloxicam	gallopamil
Meloxicam	flunarizine
Meloxicam	pimozide
Parecoxib	nimodipine
Parecoxib	nicardipine
Parecoxib	nifedipine
Parecoxib	amolodipine
Parecoxib	isradipine
Parecoxib	diltiazem
Parecoxib	verapamil
Parecoxib	bepridil
Parecoxib	gallopamil
Parecoxib	flunarizine
Parecoxib	pimozide
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	nimodipine
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	nicardipine
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	nifedipine
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	amolodipine
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	isradipine
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	diltiazem
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	verapamil
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	bepridil

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	gallopamil
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	flunarizine
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	pimozide
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	nimodipine
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	nicardipine
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	nifedipine
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	amolodipine
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	isradipine
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	diltiazem
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	verapamil
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	bepridil
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	gallopamil
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	flunarizine
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	pimozide
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	nimodipine
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	nicardipine
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	nifedipine
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	amolodipine
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	isradipine
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	diltiazem
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	verapamil
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	bepridil
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	gallopamil
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	flunarizine

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	pimozide
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	nimodipine
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	nicardipine
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	nifedipine
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	amolodipine
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	isradipine
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	diltiazem
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	verapamil
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	bepridil
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	gallopamil
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	flunarizine
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	pimozide
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	nimodipine
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	nicardipine
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	nifedipine
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	amolodipine
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	isradipine
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	diltiazem

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	verapamil
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	bepridil
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	gallopamil
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	flunarizine
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	pimozide
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	nimodipine
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	nicardipine
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	nifedipine
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	amolodipine
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	isradipine
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	diltiazem
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	verapamil
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	bepridil
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	gallopamil
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	flunarizine
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	pimozide
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	nimodipine
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	nicardipine

Cyclooxygenase-2 Selective Inhibitor	Calcium Modulating Agent
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	nifedipine
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	amolodipine
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	isradipine
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	diltiazem
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	verapamil
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	bepridil
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	gallopamil
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	flunarizine
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	pimozide
Lumiracoxib	nimodipine
Lumiracoxib	nicardipine
Lumiracoxib	nifedipine
Lumiracoxib	amolodipine
Lumiracoxib	isradipine
Lumiracoxib	diltiazem
Lumiracoxib	verapamil
Lumiracoxib	bepridil
Lumiracoxib	gallopamil
Lumiracoxib	flunarizine
Lumiracoxib	pimozide

DIAGNOSIS OF A VASO-OCCLUSION

[0464] One aspect of the invention encompasses diagnosing a subject in need of treatment or prevention for a vaso-occlusive event. A number of suitable methods for diagnosing a vaso-occlusion may be used in the practice of the invention. In one such method, ultrasound may be employed. This method examines the blood flow in the major arteries and veins in the arms and legs with the use of ultrasound (high-frequency sound waves). In one embodiment, the test may combine Doppler® ultrasonography, which uses audio measurements to "hear" and measure the blood flow and duplex ultrasonography, which provides a visual image. In an alternative embodiment, the test may utilize multifrequency ultrasound or multifrequency transcranial Doppler® (MTCD) ultrasound.

[0465] Another method that may be employed encompasses injection of the subject with a compound that can be imaged. In one alternative of this embodiment, a small

amount of radioactive material is injected into the subject and then standard techniques that rely on monitoring blood flow to detect a blockage, such as magnetic resonance direct thrombus imaging (MRDTI), may be utilized to image the vaso-occlusion. In an alternative embodiment, ThromboView® (commercially available from Agenix Limited) uses a clot-binding monoclonal antibody attached to a radiolabel. In addition to the methods identified herein, a number of other suitable methods known in the art for diagnois of vaso-occlusive events may be utilized.

INDICATIONS TO BE TREATED OR PREVENTED

[0466] The combination comprising a therapeutically effective amount of a cyclooxygenase-2 selective inhibitor and a therapeutically effective amount of a calcium modulating agent may be employed to treat or prevent a number of vaso-occlusive events or related disorders.

[0467] In some aspects, the invention provides a method to treat a central nervous system cell to prevent damage in response to a decrease in blood flow to the cell resulting from a vaso-occlusive event. Typically the severity of damage that may be prevented will depend in large part on the degree of reduction in blood flow to the cell and the duration of the reduction. By way of example, the normal amount of perfusion to brain gray matter in humans is about 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs when the flow of blood falls below approximately 8-10 mL/100 g of brain tissue/min, while at slightly higher levels (i.e. 20-35 mL/100 g of brain tissue/min) the tissue remains alive but not able to function. In one embodiment, apoptotic or necrotic cell death may be prevented. In still a further embodiment, ischemic-mediated damage, such as cytoxic edema or central nervous system tissue anoxemia, may be prevented. In each embodiment, the central nervous system cell may be a spinal cell or a brain cell.

[0468] Another aspect encompasses administrating the composition to a subject to treat a central nervous system ischemic condition resulting from a vaso-occlusive event. In one embodiment, the ischemic condition is a stroke that results in ischemic central nervous system damage, such as apoptotic or necrotic cell death, cytoxic edema or central nervous system tissue anoxemia. The stroke may impact any area of the brain or be caused by any etiology commonly known to result in the occurrence of a stroke. In one alternative of this embodiment, the stroke is a brain stem stroke. Generally speaking, brain stem strokes strike the brain stem, which control involuntary life-support functions such as breathing, blood

pressure, and heartbeat. In another alternative of this embodiment, the stroke is a cerebellar stroke. Typically, cerebellar strokes impact the cerebellum area of the brain, which controls balance and coordination. In still another embodiment, the stroke is an embolic stroke. In general terms, embolic strokes may impact any region of the brain and typically result from the blockage of an artery by a vaso-occlusion. In yet another alternative, the stroke may be a hemorrhagic stroke. Like embolic strokes, hemorrhagic stroke may impact any region of the brain, and typically result from a ruptured blood vessel characterized by a hemorrhage (bleeding) within or surrounding the brain. In a further embodiment, the stroke is a thrombotic stroke. Typically, thrombotic strokes result from the blockage of a blood vessel by accumulated deposits.

[0469] In another embodiment, the ischemic condition may result from a disorder that occurs in a part of the subject's body outside of the central nervous system, but yet still causes a reduction in blood flow to the central nervous system. These disorders may include, but are not limited to a peripheral vascular disorder, a venous thrombosis, a pulmonary embolus, a myocardial infarction, a transient ischemic attack, unstable angina, or sickle cell anemia. Moreover, the central nervous system ischemic condition may occur as result of the subject undergoing a surgical procedure. By way of example, the subject may be undergoing heart surgery, lung surgery, spinal surgery, brain surgery, vascular surgery, abdominal surgery, or organ transplantation surgery. The organ transplantation surgery may include heart, lung, pancreas or liver transplantation surgery. Moreover, the central nervous system ischemic condition may occur as a result of a trauma or injury to a part of the subject's body outside the central nervous system. By way of example the trauma or injury may cause a degree of bleeding that significantly reduces the total volume of blood in the subject's body. Because of this reduced total volume, the amount of blood flow to the central nervous system is concomitantly reduced. By way of further example, the trauma or injury may also result in the formation of a vaso-occlusion that restricts blood flow to the central nervous system.

[0470] In yet another aspect, the composition is administered to reduce infarct size of the ischemic core following a central nervous system ischemic condition. Moreover, the composition may also be beneficially administered to reduce the size of the ischemic penumbra or transitional zone following a central nervous system ischemic condition

[0471] In addition to a cyclooxygenase-2 selective inhibitor and a calcium modulating agent, the composition of the invention may also include any agent that ameliorates the effect of a reduction in blood flow to the central nervous system. In one embodiment, the agent is an anticoagulant including thrombin inhibitors such as heparin and

Factor Xa inhibitors such as warafin. In an additional embodiment, the agent is an anti-platelet inhibitor such as a GP IIb/IIIa inhibitor. Additional agents include but are not limited to, HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, and gemfibrizol; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); β-adrenergic receptor blockers; folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; and anti-oxidant vitamins such as vitamin C and E and beta carotene.

[0472] In a further aspect, the composition may be employed to reverse or lessen central nervous system cell damage following a traumatic brain or spinal cord injury. Traumatic brain or spinal cord injury may result from a wide variety of causes including, for example, blows to the head or back from objects; penetrating injuries from missiles, bullets, and shrapnel; falls; skull fractures with resulting penetration by bone pieces; and sudden acceleration or deceleration injuries. The composition of the invention may be beneficially utilized to treat the traumatic injury irrespective of its cause.

[0473] The composition may also beneficially be employed to increase recovery of neural cell function following brain or spinal cord injury. Generally speaking, when neurons are lost due to disease or trauma, they are not replaced. Rather, the remaining neurons must adapt to whatever loss occurred by altering their function or functional relationship relative to other neurons. Following injury, neural tissue begins to produce trophic repair factors, such as nerve growth factor and neuron cell adhesion molecules, which retard further degeneration and promote synaptic maintenance and the development of new synaptic connections. But, as the lost cells are not replaced, existing cells must take over some of the functions of the missing cells, i.e., they must "learn" to do something new. In part, recovery of function from brain traumatic damage involves plastic changes that occur in brain structures other than those damaged. Indeed, in many cases, recovery from brain damage represents the taking over by healthy brain regions of the functions of the damaged area. Thus the composition of the present invention may be administered to facilitate learning of new functions by uninjured brain areas to compensate for the loss of function by other regions.

EXAMPLES

[0474] A combination therapy of a COX-2 selective inhibitor and a calcium modulating agent for the treatment or prevention of a vaso-occlusive event or a related disorder in a subject can be evaluated as described in the following tests detailed below.

[0475] A particular combination therapy comprising a calcium modulating agent and a COX-2 inhibitor can be evaluated in comparison to a control treatment such as a placebo treatment, administration of a COX-2 inhibitor only, or administration of a calcium modulating agent only. By way of example, a combination therapy may contain any of the calcium modulating agents and COX-2 inhibitors detailed in the present invention, including the combinations set forth in Tables 4, 5, or 6 may be tested as a combination therapy. The dosages of a calcium modulating agent and COX-2 inhibitor in a particular therapeutic combination may be readily determined by a skilled artisan conducting the study. The length of the study treatment will vary on a particular study and can also be determined by one of ordinary skill in the art. By way of example, the combination therapy may be administered for 4 weeks. The calcium modulating agent and COX-2 inhibitor can be administered by any route as described herein, but are preferably administered orally for human subjects.

EXAMPLE 1-Evaluation of COX-1 and COX-2 activity *in vitro*

[0476] The COX-2 inhibitors suitable for use in this invention exhibit selective inhibition of COX-2 over COX-1 when tested *in vitro* according to the following activity assays.

PREPARATION OF RECOMBINANT COX BACULOVIRUSES

[0477] Recombinant COX-1 and COX-2 are prepared as described by Gierse et al, [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 is cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses are isolated by transfecting 4 μg of baculovirus transfer vector DNA into SF9 insect cells ($2x10^8$) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses are purified by three rounds of plaque purification and high titer (10^7-10^8 pfu/mL) stocks of

virus are prepared. For large scale production, SF9 insect cells are infected in 10 liter fermentors (0.5 x 106/mL) with the recombinant baculovirus stock such that the multiplicity of infection is 0.1. After 72 hours the cells are centrifuged and the cell pellet is homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate is centrifuged at 10,000xG for 30 minutes, and the resultant supernatant is stored at -80°C before being assayed for COX activity.

ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0478] COX activity is assayed as PGE2 formed/μg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 μM). Compounds are pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after ten minutes at 37°C by transferring 40 μl of reaction mix into 160 μl ELISA buffer and 25 μM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

FAST ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0479] COX activity is assayed as PGE2 formed/μg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2 μM phenol, 1 μM heme, 300 μM epinephrine) with the addition of 20 μl of 100 μM arachidonic acid (10 μM). Compounds are pre-incubated with the enzyme for 10 minutes at 25°C prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after two minutes at 37°C by transferring 40 μl of reaction mix into 160 μl ELISA buffer and 25 μM indomethacin. Indomethacin, a non-selective COX-2/COX-1 inhibitor, may be utilized as a positive control. The PGE_2 formed is typically measured by standard ELISA technology utilizing a PGE2 specific antibody, available from a number of commercial sources.

[0480] Each compound to be tested may be individually dissolved in 2 ml of dimethyl sulfoxide (DMSO) for bioassay testing to determine the COX-1 and COX-2

inhibitory effects of each particular compound. Potency is typically expressed by the IC_{50} value expressed as g compound/ml solvent resulting in a 50% inhibition of PGE2 production. Selective inhibition of COX-2 may be determined by the IC_{50} ratio of COX-1/COX-2.

[0481] By way of example, a primary screen may be performed in order to determine particular compounds that inhibit COX-2 at a concentration of 10 ug/ml. The compound may then be subjected to a confirmation assay to determine the extent of COX-2 inhibition at three different concentrations (e.g., 10 ug/ml, 3.3 ug/ml and 1.1 ug/ml). After this screen, compounds can then be tested for their ability to inhibit COX-1 at a concentration of 10 ug/ml. With this assay, the percentage of COX inhibition compared to control can be determined, with a higher percentage indicating a greater degree of COX inhibition. In addition, the IC_{50} value for COX-1 and COX-2 can also be determined for the tested compound. The selectivity for each compound may then be determined by the IC_{50} ratio of COX-1/COX-2, as set-forth above.

EXAMPLE 2-METHODS FOR MEASURING PLATELET AGGREGATION AND PLATELET ACTIVATION MARKERS

[0482] The following studies can be performed in human subjects or laboratory animal models, such as mice. Prior to the initiation of a clinical study involving human subjects, the study should be approved by the appropriate Human Subjects Committee and subjects should be informed about the study and give written consent prior to participation.

[0483] Platelet activation can be determined by a number of tests available in the art. Several such tests are described below. In order to determine the effectiveness of the treatment, the state of platelet activation is evaluated at several time points during the study, such as before administering the combination treatment and once a week during treatment. The exemplary procedures for blood sampling and the analyses that can be used to monitor platelet aggregation are listed below.

PLATELET AGGREGATION STUDY

[0484] Blood samples are collected from an antecubital vein via a 19-gauge needle into two plastic tubes. Each sample of free flowing blood is collected through a fresh venipuncture site distal to any intravenous catheters using a needle and Vacutainer hood into 7 cc vacutainer tubes (one with CTAD (dipyridamole), and the other with 3.8% trisodium citrate). If blood is collected simultaneously for any other studies, it is preferable that the platelet sample be obtained second or third, but not first. If only the platelet sample is

collected, the initial 2-3 cc of blood is discharged and then the vacutainer tube is filled. The venipuncture is adequate if the tube fills within 15 seconds. All collections are performed by trained personnel.

[0485] After the blood samples for each subject have been collected into two Vacutainer tubes, they are immediately, but gently, inverted 3 to 5 times to ensure complete mixing of the anticoagulant. Tubes are not shaken. The Vacutainer tubes are filled to capacity, since excess anticoagulant can alter platelet function. Attention is paid to minimizing turbulence whenever possible. Small steps, such as slanting the needle in the Vacutainer to have the blood run down the side of tube instead of shooting all the way to the bottom, can result in significant improvement. These tubes are kept at room temperature and transferred directly to the laboratory personnel responsible for preparing the samples. The Vacutainer tubes are not chilled at any time.

[0486] Trisodium citrate (3.8%) and whole blood is immediately mixed in a 1:9 ratio, and then centrifuged at 1200 g for 2.5 minutes, to obtain platelet-rich plasma (PRP), which is kept at room temperature for use within 1 hour for platelet aggregation studies. Platelet count is determined in each PRP sample with a Coulter Counter ZM (Coulter Co., Hialeah, Fla.). Platelet numbers are adjusted to 3.50×10^{8} /ml for aggregation with homologous platelet-poor plasma. PRP and whole blood aggregation tests are performed simultaneously. Whole blood is diluted 1:1 with the 0.5 ml PBS, and then swirled gently to mix. The cuvette with the stirring bar is placed in the incubation well and allowed to warm to 37°C for 5 minutes. Then the samples are transferred to the assay well. An electrode is placed in the sample cuvette. Platelet aggregation is stimulated with 5 μM ADP, 1 μg/ml collagen, and 0.75 mM arachidonic acid. All agonists are obtained, e.g., from Chronolog Corporation (Hawertown, Pa.). Platelet aggregation studies are performed using a Chrono-Log Whole Blood Lumi-Aggregometer (model 560-Ca). Platelet aggregability is expressed as the percentage of light transmittance change from baseline using platelet-poor plasma as a reference at the end of recording time for plasma samples, or as a change in electrical impedance for whole blood samples. Aggregation curves are recorded for 4 minutes and analyzed according to internationally established standards using Aggrolink® software.

[0487] Aggregation curves of subjects receiving a combination therapy containing a calcium modulating agent and a COX-2 inhibitor can then be compared to the aggregation curves of subjects receiving a control treatment in order to determine the efficacy of said combination therapy.

WASHED PLATELETS FLOW CYTOMETRY

[0488] Venous blood (8 ml) is collected in a plastic tube containing 2 ml of acid-citrate-dextrose (ACD) (7.3 g citric acid, 22.0 g sodium citrate x $2H_2O$ and 24.5 glucose in 1000 ml distilled water) and mixed well. The blood-ACD mixture is centrifuged at 1000 r.p.m. for 10 minutes at room temperature. The upper 2/3 of the platelet-rich plasma (PRP) is then collected and adjusted to pH=6.5 by adding ACD. The PRP is then centrifuged at 3000 r.p.m. for 10 minutes. The supernatant is removed and the platelet pellet is gently resuspended in 4 cc of the washing buffer (10 mM Tris/HCl, 0.15 M NaCl, 20 mM EDTA, pH=7.4). Platelets are washed in the washing buffer, and in TBS (10 mM Tris, 0.15 M NaCl, pH=7.4). All cells are then divided into the appropriate number of tubes. By way of example, if 9 different surface markers are evaluated, as described herein, then the cells should be divided into ten tubes, such that nine tubes containing washed platelets are incubated with 5 µl fluorescein isothiocyanate (FITC)-conjugated antibodies in the dark at +4°C for 30 minutes, and one tube remains unstained and serves as a negative control. Surface antigen expression is measured with monoclonal murine anti-human antibodies, such as CD9 (p24); CD41a (IIb/IIIa, aIIbb3); CD42b (Ib); CD61(IIIa) (DAKO Corporation, Carpinteria, Calif.); CD49b (VLA-2, or a2b1); CD62p (P-selectin); CD31 (PECAM-1); CD 41b (IIb); and CD51/CD61 (vitronectin receptor, avb3) (PharMingen, San Diego Calif.), as the expression of these antigens on the cells is associated with platelet activation. After incubation, the cells are washed with TBS and resuspended in 0.25 ml of 1% paraformaldehyde. Samples are stored in the refrigerator at +4°C, and analyzed on a Becton Dickinson FACScan flow cytometer with laser output of 15 mw, excitation at 488 nm, and emission detection at 530+-30 nm. The data can be collected and stored in list mode, and then analyzed using CELLQuest® software. FACS procedures are described in detail in, e.g., Gurbel, P. A. et al., *J Amer Coll Cardiol* 31: 1466-1473 (1998); Serebruany, V. L. et al., *Am Heart J* 136: 398-405 (1998); Gurbel, P. A. et al., *Coron Artery Dis* 9: 451-456 (1998) and Serebruany, V. L. et al., *Arterioscl Thromb Vasc Biol* 19: 153-158 (1999).

[0489] The antibody staining of platelets isolated from subjects receiving a combination therapy can then be compared to the staining of platelets isolated from subjects receiving a control treatment in order to determine the effect of the combination therapy on platelets.

WHOLE BLOOD FLOW CYTOMETRY

[0490] Four cc of blood is collected in a tube, containing 2 cc of acid-citrate-dextrose (ACD, see previous example) and mixed well. The buffer, TBS (10 mM Tris, 0.15 M NaCl, pH 7.4) and the following fluorescein isothiocyanate (FITC) conjugated monoclonal antibodies (PharMingen, San Diego, Calif., USA, and DAKO, Calif., USA) are removed from a refrigerator and allowed to warm at room temperature (RT) prior to their use. The non-limiting examples of antibodies that can be used include CD41 (IIb/IIIa), CD31 (PECAM-1), CD62p (P-selectin), and CD51/61 (Vitronectin receptor). For each subject, six amber tubes (1.25 ml) are one Eppendorf tube (1.5 ml) are obtained and marked appropriately. 450 µl of TBS buffer is pipetted to the labeled Eppendorf tube. A patient's whole blood tube is inverted gently twice to mix, and 50 µl of whole blood is pipetted to the appropriately labeled Eppendorf tube. The Eppendorf tube is capped and the diluted whole blood is mixed by inverting the Eppendorf tube gently two times, followed by pipetting 50 µl of diluted whole blood to each amber tube. 5 µl of appropriate antibody is pipetted to the bottom of the corresponding amber tube. The tubes are covered with aluminum foil and incubated at 4°C for 30 minutes. After incubation, 400 µl of 2% buffered paraformaldehyde is added. The amber tubes are closed with a lid tightly and stored in a refrigerator at 4°C until the flow cytometric analysis. The samples are analyzed on a Becton Dickinson FACScan flow cytometer. These data are collected in list mode files and then analyzed. As mentioned in (B.), the antibody staining of platelets isolated from subjects receiving a combination therapy can then be compared to the staining of platelets isolated from subjects receiving a control treatment.

ELISA

[0491] Enzyme-linked immunosorbent assays (ELISA) are used according to standard techniques and as described herein. Eicosanoid metabolites may be used to determine platelet aggregation. The metabolites are analyzed due to the fact that eicosanoids have a short half-life under physiological conditions. Thromboxane B2 (TXB_2), the stable breakdown product of thromboxane A_2 and 6keto-PGF_1 alpha, the stable degradation product of prostacyclin may be tested. Thromboxane B2 is a stable hydrolysis product of TXA_2 and is produced following platelet aggregation induced by a variety of agents, such as thrombin and collagen. 6keto-prostaglandin F_1 alpha is a stable hydrolyzed product of unstable PGI_2 (prostacyclin). Prostacyclin inhibits platelet aggregation and induces vasodilation. Thus,

quantitation of prostacyclin production can be made by determining the level of 6keto-PGF_1. The metabolites may be measured in the platelet poor plasma (PPP), which is kept at -4°C. Also, plasma samples may also be extracted with ethanol and then stored at –80° C before final prostaglandin determination, using, e.g., TiterZymes® enzyme immunoassays according to standard techniques (PerSeptive Diagnostics, Inc., Cambridge, Mass., USA). ELISA kits for measuring TXB_2 and 6keto-PGF_1 are also commercially available.

[0492] The amounts of TXB_2 and 6keto-PGF_1 in plasma of subjects receiving a combination therapy and subjects receiving a control therapy can be compared to determine the efficacy of the combination treatment.

CLOSURE TIME MEASURED WITH THE DADE BEHRING PLATELET FUNCTION ANALYZER, PFA-100®

[0493] PFA-100® can be used as an *in vitro* system for the detection of platelet dysfunction. It provides a quantitative measure of platelet function in anticoagulated whole blood. The system comprises a microprocessor-controlled instrument and a disposable test cartridge containing a biologically active membrane. The instrument aspirates a blood sample under constant vacuum from the sample reservoir through a capillary and a microscopic aperture cut into the membrane. The membrane is coated with collagen and epinephrine or adenosine 5'-diphosphate. The presence of these biochemical stimuli, and the high shear rates generated under the standardized flow conditions, result in platelet attachment, activation, and aggregation, slowly building a stable platelet plug at the aperture. The time required to obtain full occlusion of the aperture is reported as the "closure time," which normally ranges from one to three minutes.

[0494] The membrane in the PFA-100® test cartridge serves as a support matrix for the biological components and allows placement of the aperture. The membrane is a standard nitrocellulose filtration membrane with an average pore size of 0.45 μm. The blood entry side of the membrane was coated with 2 μg of fibrillar Type I equine tendon collagen and 10 μg of epinephrine bitartrate or 50 μg of adenosine 5'-diphosphate (ADP). These agents provide controlled stimulation to the platelets as the blood sample passes through the aperture. The collagen surface also served as a well-defined matrix for platelet deposition and attachment.

[0495] The principle of the PFA-100® test is very similar to that described by Kratzer and Born (Kratzer, et al., *Haemostasis* 15: 357-362 (1985)). The test utilizes whole

blood samples collected in 3.8% of 3.2% sodium citrate anticoagulant. The blood sample is aspirated through the capillary into the cup where it comes in contact with the coated membrane, and then passes through the aperture. In response to the stimulation by collagen and epinephrine or ADP present in the coating, and the shear stresses at the aperture, platelets adhere and aggregate on the collagen surface starting at the area surrounding the aperture. During the course of the measurement, a stable platelet plug forms that ultimately occludes the aperture. The time required to obtain full occlusion of the aperture is defined as the "closure time" and is indicative of the platelet function in the sample. Accordingly, "closure times" can be compared between subjects receiving a combination therapy and the ones receiving a control therapy in order to evaluate the efficacy of the combination treatment.

EXAMPLE-3

[0496] The laboratory animal study can generally be performed as described in Tanaka *et al.*, *Neurochemical Research*, Vol. 20, No. 6, 1995, pp. 663-667.

[0497] Briefly, the study can be performed with about 30 gerbils, with body weights of 65 to 80 grams. The animals are anesthetized with ketamine (100mg/kg body weight, i.p.), and silk threads are placed around both common carotid arteries without interrupting carotid artery blood flow. On the next day, bilateral common carotid arteries are exposed and then occluded with surgical clips after light ether anesthesia (*see*, e.g., Ogawa *et al.*, *Adv. Exp. Med. Biol.*, 287:343-347, and Ogawa *et al.*, *Brain Res.*, 591:171-175). Carotid artery blood flow is restored by releasing the clips after 5 minutes of occlusion. Body temperature is maintained about 37°C using a heating pad and an incadescent lamp. Control animals are operated on in a similar manner but the carotid arteries are not occluded. The combination therapy is administered immediately and 6 and 12 hours after recirculation in the ischemia group, whereas sham-operated animals receive placebo, which may be, e.g., the vehicle used to administer the combination therapy. Gerbils are sacrificed by decapitation 14 days after recirculation. The brain is removed rapidly and placed on crushed dry-ice to freeze the tissue.

[0498] The brain tissue can then be examined histologically for the effects of combination therapy in comparison to the placebo. For example, each brain is cut into 14 μm thick sections at -15°C. Coronal sections that include the cerebral cortex and hippocampal formation are thawed, mounted onto gelatin-coated slides, dried completely, and fixed with 10% formalin for 2 hours. The sections are stained with hematoxylin-eosin and antibodies to

glial fibrillary acidic protein (GFAP), which can be commercially obtained from, e.g., Nichirei, Tokyo, Japan. Immune complexes are detected by the avidin-biotin interaction and visualized with 3,3'-diaminobenzidine tetrahydrochloride. Sections that are used as controls are stained in a similar manner without adding anti-GFAP antibody. The densities of living pyramidal cells and GFAP-positive astrocytes in the typical CA1 subfield of the hippocampus are calculated by counting the cells and measuring the total length of the CA1 cell layer in each section from 250x photomicrographs. The average densities of pyramidal cells and GFAP-positive astrocytes in the CA1 subfield for each gerbil are obtained from counting cells in one unit area in each of these sections of both left and right hemispheres.

[0499] The effects of the combination therapy in comparison with the placebo can be determined both qualitatively and quantitatively. For example, the appearance of CA1 pyramidal neurons and pyramidal cell density in the CA1 subfield may be used to assess the efficacy of the treatment. In addition, immunohistological analysis can reveal the efficacy of combination by evaluating the presence or absence of hypertrophic GFAP-positive astrocytes in the CA1 region of treated gerbils, since the sham-operated animals should have few GFAP-positive astrocytes.

EXAMPLE 4

[0500] Rat middle cerebral artery occlusion (MCAO) models are well known in the art and useful in assessing a neuroprotective drug efficacy in stroke. By way of example, the methods and materials for MCAO model described in Turski *et al.* (*Proc. Natl. Acad, Sci. USA*, Vol. 95, pp.10960-10965, Sept. 1998) may be modified for testing the combination therapy as described above for cerebral ischemia treatment.

[0501] The permanent middle cerebral artery occlusion can be established by means of microbipolar permanent coagulation in, e.g., Fisher 344 rats (260-290 grams) anesthetized with halothane as described previously in, e.g., Lippert *et al.*, *Eur. J. Pharmacol.*, 253, pp.207-213, 1994. To determine the efficacy of the combination treatment and the therapeutic window for such treatment, the combination therapy can be administered, e.g., intravenously over 6 hours beginning 1, 2, 4, 5, 6, 7, 12, or 24 hours after MCAO. It should be noted that different doses, routes of administrations, and times of administration can also be readily tested. Furthermore, the experiment should be controlled appropriately, e.g. by administering placebo to a set of MCAO-induced rats. To evaluate the efficacy of the combination therapy, the size of infarct in the brain can be estimated stereologically, e.g., seven days after MCAO, by means of advanced image analysis.

[0502] In addition, the assessment of neuroprotective action against focal cerebral reperfusion ischemia can be performed in Wistar rats (250-300 grams) that are anesthetized with halothane and subjected to temporary occlusion of the common carotid arteries and the right middle cerebral artery (CCA/MCAO) for 90 minutes. CCAs can be occluded by means of silastic threads placed around the vessels, and MCA can be occluded by means of a steel hook attached to a micromanipulator. Blood flow stop can be verified by microscopic examination of the MCA or laser doppler flowmetry. Different doses of combination therapy can then be administered over, e.g., 6 hours starting immediately after the beginning of reperfusion or, e.g., 2 hours after the onset of reperfusion. As mentioned previously, the size of infarct in the brain can be estimated, for example, stereologically seven days after CCA/MCAO by means of image analysis.

EXAMPLE-5

[0503] The following procedures can be performed as described in, e.g., Nogawa *et al.*, *Journal of Neuroscience*, 17(8):2746-2755, April 15, 1997.

[0504] The middle cerebral artery (MCA) is transiently occluded in a number of Sprague Dawley rats, weighing 275-310 grams, using an intravascular occlusion model, as described in, e.g., Longa *et al.*, *Stroke* 20:84-91, 1989, Iadecola *et al.*, *Stroke* 27:1373-1380, 1996,and Zhang *et al.*, *Stroke* 27:317-323. A skilled artisan can readily determine the appropriate number of animals to be used for a particular experiment. Under halothane anesthesia (induction 5%, maintenance 1%), a 4-0 nylon monofilament with a rounded tip is inserted centripetally into the external carotid artery and advanced into the internal carotid artery until it reaches the circle of Willis. Throughout the procedure, body temperature is maintained at 37° ± 0.5°C by a thermostatically controlled lamp. Two hours after induction of ischemia, rats are reanesthetized, and the filament is withdrawn, as described in, e.g., Zhang *et al.*, *Stroke* 27:317-323. Animals are then returned to their cages and closely monitored until recovery from anesthesia.

[0505] Under halothane anesthesia, the femoral artery is cannulated, and rats are placed on a stereotaxic frame. The arterial catheter is used for monitoring of arterial pressure and other parameters at different times after MCA occlusion. The MCA is occluded for 2 hours, as described above, and treatments are started, e.g., 6 hours after induction of ischemia. In one group of rats (e.g., 6), the combination therapy is administered, e.g., intraperitoneally, twice a day for 3 days. It should be noted that different doses, routes of

administration, and times of administration can also be readily tested. A second group of rats is treated with a placebo administered in the same manner. Arterial pressure, rectal temperature, and plasma glucose are measured three times a day during the experiment. Arterial hematocrit and blood gases are measured before injection and 24, 48, and 72 hours after ischemia. Three days after MCA occlusion, brains are removed and frozen in cooled isopentane (-30°C). Coronal forebrain sections (30μM thick) are serially cut in cryostat, collected at 300 μm intervals, and stained with thionin for determination of infarct volume by an image analyzer (e.g., MCID, Imaging Research), as described in Iadecola *et al., J Cereb Blood Flow Metab*, 15:378-384, 1995. Infarct volume in cerebral cortex is corrected for swelling according to the method of Lin *et al., Stroke* 24:117-121, 1993, which is based on comparing the volumes of neocortex ipsilateral and contralateral to the stroke. The correction for swelling is needed to factor out the contribution of ischemic swelling to the total volume of the lesion (see Zhang and Iadecola, *J Cereb Blood Flow Metab*, 14:574-580, 1994). Reduction of infarct size in combination therapy-treated animals compared to animals receiving placebo is indicative of the efficacy of the combination therapy.

[0506] It should be noted that all of the above-mentioned procedures can be modified for a particular study, depending on factors such as a drug combination used, length of the study, subjects that are selected, etc. Such modifications can be designed by a skilled artisan without undue experimentation.